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British Medical Bulletin

Tuberculosis

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BOOK REVIEWS

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Scientific Editor: *J. G. Scadding*

Progress in Tuberculosis

This number contains an account of current therapeutic procedures in the field of human tuberculosis, as well as of some recent achievements in research and the fresh problems that they have produced.

In many industrialized countries there was a tendency for the general tuberculosis death-rate to mount during the epoch of their initial industrialization, which, when it occurred in the eighteenth or nineteenth centuries, was accompanied by overcrowding, bad working conditions, and other environmental factors conducive to the spread of infection from the large reservoir already existent in the towns; the peak was then reached, and, as social conditions improved, a gradual decline took place, interrupted by national catastrophes such as wars. The fall in mortality proceeded apace even before the causative organism was discovered in 1882. General public health measures may have had some effect before this date, and more particular preventive procedures, stemming from knowledge of contagion in this disease, probably did so afterwards; but it is unlikely that specific therapeutic measures played any considerable part, at least in

Britain, until after 1920 when radiographic detection and control became accurate, and collapse treatment improved the prognosis for selected patients. During the past decade, tremendous acceleration in the fall of the tuberculosis death-rate in many countries has followed the introduction of efficient chemotherapy and greatly improved surgical measures. This decline has thrown into prominence the very much slower fall in rate of notification of new cases, a fact which suggests that while we are probably missing fewer cases now, we are not making the same progress with prevention as we are with treatment. In case there is a temptation to be complacent, it may be noted, too, that some 350,000 known cases of tuberculosis are on clinic registers in Great Britain, one of the more favourably placed countries, and that this disease is still one of the main killing and incapacitating conditions affecting people of working age. Some of these subjects are discussed by J. C. McDonald & V. H. Springett in their analysis of the trends of tuberculosis mortality in western Europe during the present century.

When effective chemotherapy for certain bacterial infections was first discovered, it was expected that the mycobacterial diseases would prove especially difficult. Although some of the presumed obstacles, e.g., a "lipid barrier" of the tubercle bacillus, turned out to be exaggerated—for we now have a series of valuable water-soluble drugs—tuberculosis still offers a large field for chemotherapeutic research. After a drug has shown promise in the laboratory, its establishment as clinically valuable in this chronic and fluctuating disease is itself a research problem. The building up of a method of controlled trial in tuberculosis by co-operative effort, under the auspices of the Medical Research Council, is described by W. Fox. The need for such trials is exemplified by the uncertainty that had previously surrounded the question of the place of *p*-aminosalicylic acid in treatment. By such clinical-statistical procedures it has been possible rapidly to provide a balanced guide for action in individual cases, and this is outlined by J. G. Scadding for the current combinations of antituberculosis drugs. Each new drug has, however, brought its problems, and outstanding amongst these is drug resistance, which is discussed by D. A. Mitchison. Not only is this problem of great practical importance, but its study has led to fundamental observations in the field of bacterial genetics.

Undoubtedly chemotherapy predominates among therapeutic measures at the present time, both in its own right and in enabling surgical procedures to be carried out with greater safety. Improved techniques of chest surgery have coincided with these advances, as H. R. S. Harley describes, and surgical methods have recently been extended to clinical primary tuberculosis. The impact also of chemotherapy on the management of bone and joint tuberculosis is apparent from M. C. Wilkinson's article. There is, of course, a danger of the pendulum swinging too far, and the virtual abandonment of artificial pneumothorax by many may be ultimately regretted; this is suggested by the unique long-term follow-up study of artificial pneumothorax described by A. F. Foster-Carter, who holds that in selected cases this treatment, supplemented by chemotherapy, still has an important place.

With the ability to treat efficiently a large variety of acute and chronic forms of tuberculosis, it is increasingly important to detect as many cases as possible, and A. L. Cochrane looks to the future when he shows that by determined action nearly all the cases of pulmonary tuberculosis in a community may be discovered. Early diagnosis is as imperative as ever and especially in tuberculous meningitis, so that the contribution by H. V. Smith & R. L. Vollum should be of particular value. After diagnosis and treatment, there is the pressing problem of rehabilitating both the infective and non-infective patients who are fit to return to industry; and R. Grenville-Mathers discusses the special difficulties of these people, describes the present provisions, and indicates some further measures whereby their lot could be improved so that they could more often again become productive members of the community. The modern chest clinic, which has evolved from Robert Philip's specialist dispensary for the tuberculous, established in Edinburgh in 1887, has become increasingly the focus for all services responsible for the care of the patient and his family, both medically and socially; and B. R. Clarke describes its development and present functions, giving a critical review of the changes made by the National Health Service Act of 1946. As the age-range over which primary infection occurs has been gradually extending, interest in primary disease is growing, and its sources, clinical manifestations and more immediate sequels, and its treatment, are discussed by J. Crofton.

Prevention of tuberculosis by vaccination has been a subject of controversy ever since *Bacille Calmette Guérin* (BCG) was first used in man; and no attempt is made in this number to assess the degree of efficacy of this measure. Wide experience of BCG has given virtual certainty of its safety. However, the vole bacillus, discovered by Wells in 1937, has experimental properties that may give it some advantages over BCG. A. Q. Wells & J. A. H. Wylie point out that the vole bacillus is a natural pathogen (to voles), whose pathogenicity can be maintained by returning to its animal host, unlike BCG which is an artificially attenuated strain. Moreover, animal experiments suggest that the immunity may exceed in degree and duration that given by BCG. A Medical Research Council clinical trial is in progress to assess the merits of the two vaccines in protection.

The current interest in chemotherapy and in vaccination against tuberculosis makes it even more important to understand the relationship between host and parasite in this infection. New light is being thrown upon the role of the monocyte (macrophage) in defence by the technique of surviving-cell preparations devised by G. B. Mackaness. This author describes the growth of tubercle bacilli of varying virulence in these phagocytic host cells, isolated both from normal and from immun-

ized animals; he criticizes the prevailing view that interference with growth and life of bacilli ingested by monocytes is a feature of acquired immunity and native resistance. Another important aspect of the host-parasite relationship is discussed by R. J. W. Rees, who describes how it has been possible recently to affect the host's defence mechanisms by chemical means. Thus cortisone strikingly enhances host susceptibility to tuberculous infection in some species ; while a series of non-ionic surface-active polyoxyethylene ethers have been discovered at the National Institute for Medical Research to be strongly suppressive in experimental tuberculosis, although they are not bacteriostatic in vitro. The latter finding has suggested a search for other agents that may be of chemotherapeutic use through increasing host resistance, in contrast to the direct antibacterial action of the drugs in current use in tuberculosis. This work may also provide information on some of the natural defence mechanisms against this infection.

The different topics covered by our contributors thus reflect the large variety of factors that can be operative in reducing human tuberculosis—ranging from purely medical measures such as immunization and chemotherapy to the basic influence of general social advance. Indeed, there is no branch of medicine attracting greater activity at the present time. It should be our aim that the benefits of this activity be shared by all countries.

P. D'Arcy Hart

We are grateful to Dr P. D'Arcy Hart for acting as Chairman of the planning committee and for much help in arranging this symposium.

Notes on Contributors

DR BRICE R. CLARKE was Medical Superintendent of Forster Green Hospital, Belfast, Northern Ireland, from 1925 to 1941, when he became Medical Superintendent of the Belfast Municipal Sanatorium, and, in 1940, Chief Tuberculosis Officer for the city of Belfast. He held both these posts until 1946, when he was appointed Director of the Northern Ireland Tuberculosis Authority. He relinquished this appointment in 1950, when he was made Consultant Physician to the Northern Ireland Tuberculosis Authority. He is Consultant to a chest hospital and a children's hospital, and is responsible for chest clinics in most of the Belfast area of Northern Ireland. Dr Clarke was formerly a member of the Joint Tuberculosis Council, of the Council of the British Tuberculosis Association, of the Council of the Northern Ireland Branch of the British Medical Association, and of the Medical Advisory Council (Northern Ireland); he is a corresponding member of the tuberculosis section of the World Health Organization, and of the Société Française de la Tuberculose. Dr Clarke's publications include *Causes and prevention of tuberculosis* (1952), a chapter on phthisis in Whitla's *Dictionary of treatment* (8th ed., 1938), and an article, written jointly with S. L. W. Erskine, on late results of artificial pneumothorax in pulmonary tuberculosis (*Quart. J. Med.* 1940, n.s. **9**, 323).

DR A. L. COCHRANE has been a member of the Medical Research Council's Pneumoconiosis Research Unit since 1948. He became deeply interested in the prevention of tuberculosis as a result of his experience as a physician in prisoner-of-war camps in Germany during the Second World War. After the war he worked at the Henry Phipps Institute at Philadelphia as a Rockefeller Foundation Fellow, studying the errors in the detection of early tuberculosis and the prognostic value of the radiograph in these cases. Since joining the Pneumoconiosis Research Unit, he has been responsible for the surveys carried out by the Unit at mines in South Wales and in England. These surveys have greatly increased the knowledge of the natural history of coal-workers' pneumoconiosis. In 1950 he started a long-term and ambitious piece of epidemiological research to see if it was possible in a mining community of 30,000 to reduce the tuberculosis infectivity (by very complete *x*-ray surveys and immediate treatment of all cases of tuberculosis revealed) and thereby show the importance of tuberculosis in the causation of complicated pneumoconiosis. The surveys have also provided an exceptional opportunity to study the prevalence of other common diseases. His work has been published in the *British Journal of Industrial Medicine*, the *Lancet*, and the *British Medical Journal*, and in the journals in Great Britain and in the USA dealing with radiology.

PROFESSOR J. W. CROFTON is at present Professor of Tuberculosis and Director of the Department of Tuberculosis and Diseases of the Respiratory System at the University of Edinburgh, and Honorary Consultant Physician of the South-Eastern Regional Hospital Board (Scotland). From 1947 to 1951 he was Lecturer, and later Senior Lecturer, in Chest Diseases, at the Postgraduate Medical School of London, and also Physician at Hammersmith Hospital, London. From 1947 to 1949 he was a part-time member of the Medical Research Council's Tuberculosis Research Unit at the Brompton Hospital, London, where from 1949 to 1950 he was Senior Assistant of the Institute of Diseases of the Chest. Professor Crofton's clinical work was carried out in London at Hammersmith Hospital and at the Brompton Hospital, and his research work has been concerned with pneumonia, pulmonary eosinophilia and the chemotherapy of pulmonary tuberculosis. He is joint author of "Pneumonia in West London, 1949–50" (*Brit. med. J.* 1951, **2**, 1368), "Pulmonary eosinophilia" (*Thorax*, 1952, **7**, 1), and "Streptomycin resistance in patients with pulmonary tuberculosis previously treated with P.A.S. alone" (*Brit. med. J.* 1953, **1**, 1244).

DR A. F. FOSTER-CARTER is at present Medical Superintendent of Brompton Hospital Sanatorium, Frimley, Aldershot, Hampshire, and before that spent most of his time as Resident Medical Officer of Brompton Hospital, London. His previous published work mainly concerns bronchial conditions and bronchopulmonary anatomy, but for the past six years he has been engaged on an extensive follow-up study of patients discharged from the Brompton Hospital Sanatorium. His publications include articles on bronchial adenoma (*Quart. J. Med.* 1941, n.s. **10**, 139), on recent work on the anatomy of the bronchi (*Brit. med. Bull.* 1944, **2**, 37), and, with other authors, on the results of collapse and conservative therapy in pulmonary tuberculosis (*Brompton Hosp. Rep.* 1952, **21**, 1).

DR WALLACE FOX qualified in 1943, was made M.R.C.P. in 1950 and, a year later, M.D. with distinction of the University of London. He was formerly a whole-time clinical assistant in the Department of Medicine, and an assistant medical registrar at Guy's Hospital, London. From 1946 to 1950 he was a resident medical officer at Preston Hall, British Legion Village, near Maidstone, Kent, where he obtained experience of rehabilitation and of the village settlement scheme as well as of the usual sanatorium treatments; from 1949 to 1950 he was also Clinical Tutor to the undergraduate and postgraduate students. From 1951 to 1952 Dr Fox was Assistant Chest Physician at the Hammersmith Chest Clinic, London. Since May 1952, he has been a member of the Medical Research Council's Tuberculosis Research Unit, Hampstead, London; he has co-ordinated the current trials of isoniazid and has jointly analysed the results and written the reports. In addition to publications on chemotherapeutic trials, he has written several articles on pneumoperitoneum therapy.

DR R. GRENVILLE-MATHERS received his medical and scientific training at Downing College, Cambridge, and at Westminster Hospital Medical School, London, where he also carried out biochemical research. He became interested in tuberculosis while serving with the Army in India and South Africa. On returning to Great Britain he worked in a sanatorium in North Wales until, in 1947, he was appointed Consultant Tuberculosis Officer to the County Borough of Wallasey. It was while he was here that he became concerned with the subject of resettlement of the tuberculous. In 1950 he was appointed Consultant Physician in Charge of the Harrow Chest Clinic, Middlesex, and also Physician to Edgware General Hospital and Harrow Hospital. In addition he is a member of the Pneumoconiosis Medical Panel and Silicosis Medical Board, and is a Lecturer in Tuberculosis at the Chiswick Polytechnic, London. He has published a number of papers on tuberculosis and chest diseases.

MR H. R. S. HARLEY was Surgical Registrar to Guy's Hospital, London, from 1940 to 1941, and thereafter was in the Indian Medical Service until 1946. During this period he was in charge of several surgical divisions of 1,000-bedded hospitals. He was Officer Commanding the War Wounds Research Team, India Command, and Advisor in Surgery to India Command. He was at one time Chief Assistant to Sir Clement Price Thomas. At present he is Consultant Thoracic Surgeon to the United Cardiff Hospitals and to the Welsh Regional

NOTES ON CONTRIBUTORS

Hospital Board. He is joint author with J. H. Bowie & M. D. Borcar of "Penicillin therapy in late infected compound fractures from Burma" (*Brit. J. Surg.* 1947, **34**, 348), and has written articles on subphrenic abscess (*Thorax*, 1949, **4**, 1), on the treatment of acute, uncomplicated, non-tuberculous empyema, secondary to infections of the lung (*Med. Press*, 1953, **229**, 293), and on popliteal aneurysm (*Guy's Hosp. Rep.* 1940–41, **90**, 255).

DR P. D'ARCY HART has been Director of the Medical Research Council's Tuberculosis Research Unit, Hampstead, London, since its formation in 1948, and he also works at the National Institute for Medical Research, London. He joined the Council's staff in 1937, having been previously Assistant Physician to University College Hospital, London. From 1937 to 1941 he was engaged in the Council's investigation into pneumoconiosis in South Wales coal-miners, and was later secretary of its Committee on Tuberculosis in Wartime. The Unit's work has been devoted mainly to clinical trials of chemotherapy in tuberculosis and of antituberculosis vaccines, and to a national tuberculin survey. Dr Hart has also been responsible for, or collaborated in, work on the value of tuberculin tests in man, and on tuberculosis and social conditions; and, in the laboratory, on the pigments formed by streptococci, factors in host susceptibility to experimental tuberculosis, development of new series of antituberculosis chemotherapeutic agents, and virulence of the tubercle bacillus. In 1937 he gave the Milroy Lectures, and in 1946 the Mitchell Lecture, Royal College of Physicians, and was awarded its Weber-Parkes Prize in 1951. He is a member of the World Health Organization's Expert Advisory Panel on Tuberculosis.

DR J. C. MCDONALD received his medical education at St Mary's Hospital Medical School, University of London. After serving in the Royal Army Medical Corps during the Second World War, he took up the study of public health in 1948 at the London School of Hygiene and Tropical Medicine. He was awarded a Rockefeller Foundation Fellowship in 1949 and until 1951 studied epidemiology at the London School of Hygiene and Tropical Medicine and at Harvard University. He works at present in the Epidemiological Research Laboratory of the Public Health Laboratory Service at Colindale, London, where he is mainly concerned with the investigation of problems related to passive immunization and to the evaluation of influenza vaccines.

DR G. B. MACKANESS is at present Senior Fellow in the Department of Experimental Pathology in the John Curtin School of Medical Research at the Australian National University, Canberra. As Scholar and Fellow of that university he worked for five years up to the end of 1953 at the Sir William Dunn School of Pathology, Oxford. His studies have been concerned with the significance of the intracellular tubercle bacillus in its response to chemotherapeutic agents, and with the more fundamental aspect of the parasitism of tubercle bacilli. The results of these studies appear in papers published in the *Journal of Pathology and Bacteriology* and the *American Review of Tuberculosis*.

DR D. A. MITCHISON has been Lecturer in Bacteriology at the Postgraduate Medical School of London since 1948. Previously he was assistant to the Pathologist at Brompton Hospital, London. For the past seven years he has worked in close association with the Medical Research Council's Streptomycin in Tuberculosis Trials Committee, his main concerns being the development of drug resistance to streptomycin in vitro and in patients, and the measurement of streptomycin in body fluids. His present work has been connected with the trials of isoniazid planned by the Medical Research Council's Tuberculosis Chemotherapy Trials Committee, of which he is a member. He has organized a reference laboratory for these trials whose main use has been to check the accuracy of the methods for determining drug resistance and to carry out most of the PAS sensitivity tests on strains of tubercle bacilli isolated during the trials. In addition he has carried out work on the virulence of tubercle bacilli resistant to isoniazid. Dr Mitchison has published papers on these subjects in the *Journal of General Microbiology*, the *Journal of Clinical Pathology*, the *Lancet* and other medical and scientific journals.

DR R. J. W. REES has been, since 1949, on the Scientific Staff of the Medical Research Council, working at the National Institute for Medical Research, London. From 1942 to 1946 he was with the Royal Army Medical Corps in the Blood Transfusion Service. After the Second World War he returned to Guy's Hospital, London, where he worked first as Assistant Clinical Pathologist and then as University Demonstrator in the Department of Experimental Pathology and Morbid Histology. During the tenure of the latter appointment Dr Rees became interested in research on the chemotherapy of tuberculosis and, in collaboration with Professor J. M. Robson, he developed a corneal method of assessing antituberculosis drugs in the rabbit and mouse. During the last five years his work has been concerned mainly with the study of factors influencing the susceptibility of the host to tuberculosis. His published work includes accounts of these and other aspects of experimental tuberculosis.

DR J. G. SCADDING obtained his medical education at the Middlesex Hospital Medical School, University of London. After the usual junior medical appointments, he became, in 1935, First Assistant in the Department of Medicine at the British Postgraduate Medical School, now the Postgraduate Medical School of London, and was elected to the staff of Brompton Hospital, London, in 1939. At present his chief appointments are Director of Studies and Dean, Institute of Diseases of the Chest; Physician, Brompton Hospital; Senior Lecturer in Medicine, Postgraduate Medical School of London; Physician, Hammersmith Hospital, London; and Honorary Consultant in Diseases of the Chest to the Army at Home. Dr Scadding is Joint Editor of *Thorax*. His original publications have been concerned chiefly with the pneumonias and with sarcoidosis; he has published sections on various aspects of respiratory disease in a number of textbooks.

DR HONOR SMITH is May Reader in Medicine at the University of Oxford, and Physician in Charge of the Tuberculous Meningitis Unit of the Oxford United Hospitals. She is a member of the Society of British Neurological Surgeons. Dr Smith has published, with other authors, articles on "Chemotherapy of pneumococcal meningitis" (*Lancet*, 1946, **1**, 185), "Treatment of tuberculous meningitis with streptomycin" (*Lancet*, 1948, **1**, 627) and "Effects of intrathecal tuberculin and streptomycin in tuberculous meningitis: an interim report" (*Lancet*, 1950, **2**, 275).

DR V. H. SPRINGETT has, since 1945, been Prophit Scholar of the Royal College of Physicians of London, engaged in a follow-up study of small tuberculous lesions found by mass radiography; for the last three years he has also been part-time Assistant Chest Physician in the Borough of Greenwich, London. He trained at King's College, London (where he was Warneford Scholar in 1935) and King's College Hospital Medical School, London. After holding house appointments, he assisted in the final stages of field work and analysis of the first Prophit Survey, published as *Tuberculosis in young adults: report on the Prophit Tuberculosis Survey, 1935–1944* (1948). In 1949 he obtained the M.D. London, being awarded the University Gold Medal; his thesis was published under the title of "A comparative study of tuberculosis mortality rates" (*J. Hyg., Camb.* 1950, **48**, 361), and this subject was further developed in his Milroy Lectures, delivered before the Royal College of Physicians in 1952.

DR R. L. VOLLUM has, since 1926, been University Lecturer in Bacteriology in the Department of Pathology at the University of Oxford. In 1938 he was appointed Bacteriologist to the Radcliffe Infirmary, and in 1950 became Director of the Public Health Laboratory at Oxford. Dr Vollum has published, jointly with other authors, "Comparison of A.P.T. and T.A.F. for immunization of nurses against diphtheria" (*Mon. Bull. Minist. Hlth Lab. Serv.* 1947, **6**, 209), "Mutation and pathogenicity experiments with B.C.G." (*Lancet*, 1931, **1**, 9), and "Treatment of tuberculous meningitis with streptomycin" (*Lancet*, 1948, **1**, 627).

DR A. Q. WELLS was formerly Senior Demonstrator in Bacteriology and Assistant Bacteriologist at St Bartholomew's Hospital, London. He is a member of the Scientific Staff of the Medical Research Council, at present working in the Sir William Dunn School of Pathology, University of Oxford, where he is engaged in research on the immunology of tuberculosis. His past scientific work has been concerned with bacteriological research and teaching. Dr Wells is the author of the Medical Research Council's Special Report No. 259, *The murine type of tubercle bacillus (the vole acid-fast bacillus)* (1946, London), and of various papers on tuberculosis.

MR M. C. WILKINSON is Orthopaedic Surgeon to the Surgical Tuberculosis Unit at Black Notley Hospital, Braintree, Essex, and was formerly Medical Superintendent of that hospital with clinical charge of patients suffering from skeletal and other forms of non-pulmonary tuberculosis. He had previously worked at the Heritage Craft Schools and Orthopaedic Hospital, Chailey, Sussex, and at Queen Mary's Hospital for Children, Carshalton, Surrey. He is a Fellow of the British Orthopaedic Association and was a Hunterian Professor of the Royal College of Surgeons in 1948. His publications include *Non-pulmonary tuberculosis* (1942) and papers entitled "Synovectomy and curettage in the treatment of tuberculosis of joints" (*J. Bone Jt Surg.* 1953, **35-B**, 209) and "Chemotherapy of tuberculosis of bones and joints" (*J. Bone Jt Surg.* 1954, **36-B**, 23). The latter essay gained Mr Wilkinson a *proxime accessit* award for the Robert Jones Medal and British Orthopaedic Association Prize.

DR J. A. H. WYLIE studied medicine at Göttingen University, Germany, and at University College and University College Hospital, London. He was formerly Assistant Clinical Pathologist, University College Hospital, and Assistant Bacteriologist in the Emergency Public Health Laboratory Service. At present he is University Demonstrator in Pathology at the University of Oxford. His work has been concerned with routine bacteriology and pathology, teaching and research, and with field trials of vole bacillus vaccine. Dr Wylie has written various articles on experimental leptospirosis and the epidemiology and diagnosis of that disease, studies upon the pathology of sarcoidosis and tuberculosis, and reports upon the use of vole bacillus vaccine in human communities.

THE DECLINE OF TUBERCULOSIS MORTALITY IN WESTERN EUROPE

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V. H. SPRINGETT M.D.

Prophit Survey
Royal College of Physicians of London

1 The decline in crude rates
2 Causes of decline in mortality
  a Declining infection
  b Improving social conditions
  c Medical measures
3 Sex differences in mortality
4 Discussion of the changes in distribution by sex and age
References

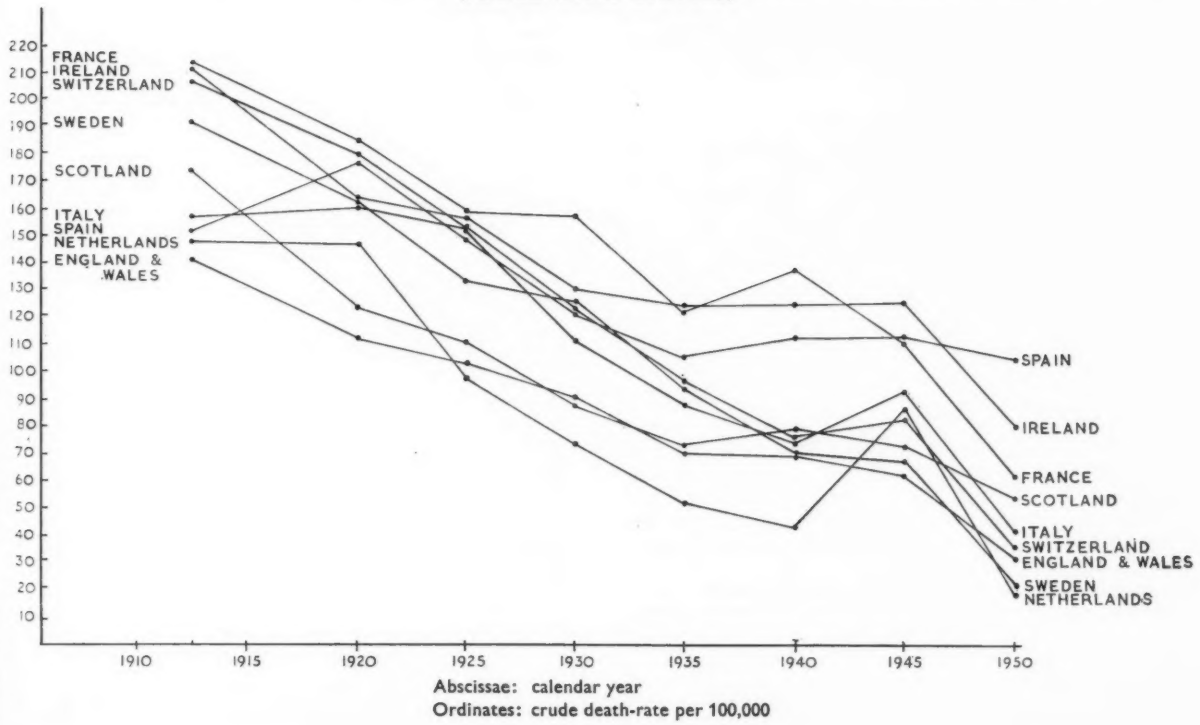
1. The Decline in Crude Rates

The magnitude of the decline in the recorded tuberculosis mortality during the past 40 years or more is so great that its reality seems certain. Nevertheless, this trend must be interpreted with caution since it is based on crude death-rates which took no account of considerable differences in the age and sex structure of the population of different countries, and upon a registration of causes of death which in many areas until recently was incomplete and inaccurate. The devastation and disorganization of two world wars rendered the picture even more obscure.

Trends for nine countries from 1911 to 1950, shown in fig. 1, show reductions ranging from 31% (in Spain) to 88% (in Sweden). With the exception of the period of the 1914–18 war (omitted from fig. 1), the rates fell steadily until 1939, when the decline became less rapid and in some countries the mortality actually increased. In a detailed study of tuberculosis mortality in Europe during the years of the Second World War, Daniels (1949) noted that the national mortality patterns reflected the deterioration of social conditions and were of three main types. In Spain, Switzerland and the Scandinavian countries there was little or no war-time rise; in England and Wales, Belgium, Eire and France the rates rose in the first years and fell in the later years of the war; in other countries, such as Holland, Germany and Italy, the death-rates rose to a peak at the end of the war. After 1946 the death-rates fell in all European countries except Scotland; within a few years they were at about the level that they would have reached if pre-war trends had continued uninterrupted.

The tuberculosis mortality since 1948 merits separate consideration. In the British Isles, Scandinavia, France,

FIG. 1. TREND OF MORTALITY FROM ALL FORMS OF TUBERCULOSIS IN WESTERN EUROPE 1911–50 (PERIOD 1914–18 OMITTED)



Abscissae: calendar year
Ordinates: crude death-rate per 100,000

Belgium, the Netherlands and Switzerland, deaths from respiratory tuberculosis fell betweeen 1948 and 1950 by more than 20%. As noted before, the rates had been declining since the end of the war, but in general the rates showed much less improvement in the interval 1945–48 than in the interval 1948–50; the rates for Scotland shared in the fall after 1948. For those countries for which rates are obtainable, the considerable fall in rate has been maintained in 1951 and 1952.

2. Causes of Decline in Mortality

In tuberculosis, as in other communicable diseases, not all persons in the community are infected, not all infected persons become ill, nor do all ill persons die; the outcome of each of these stages depends on the balance which exists between the infecting agent, the human host and the environmental factors, and a decline in mortality depends upon a change in any or all of them.

It is theoretically possible that changes in virulence of the tubercle bacillus or in the innate susceptibility of the population of Europe may have contributed to the decline in mortality observed during the past 50 years. There is, however, no evidence of any such change in the tubercle bacillus. Tuberculosis has been present in the population of Europe for centuries and it is probable that the elimination of susceptible persons has gradually produced a population more resistant than it once was, and certainly more resistant than populations exposed to tuberculosis for the first time; it seems unlikely, however, that this factor can have contributed greatly to the decline in mortality during the past 50 years. We must conclude that the environment, especially social factors, has brought about the decline either by reducing the risk of infection or by increasing the infected person's chance of survival. In a strict sense environmental conditions include available medical treatment, but it is more convenient to consider separately the influence of treatment of established cases on mortality rates.

a. Declining Infection

Reduced opportunities for infection with tubercle bacilli probably account for much of the decline in tuberculosis mortality, though precise and direct information is not available. The recent level of infection-rates at various ages is known in many countries, but adequate comparable figures for the early part of the century do not exist. The Medical Research Council survey in 1949–50 showed that in England and Wales about 15% were infected at ages 5 and 6 years, about 50% at ages 15 and 16 years and 65–70% at ages 19 and 20 years (Medical Research Council, 1952): lower figures have been recorded for Scandinavian countries. It is probable that 50 years ago very much higher proportions were infected at each age. Indirect evidence of declining primary infection in childhood is given by the fall in mortality from tuberculous meningitis and miliary tuberculosis in these age-groups. The control of infection from milk in those areas where bovine tuberculosis occurred on a large scale must have played a considerable part in lowering both the infection and mortality rates in children.[1]

Reduction of infection is perhaps best measured by the declining percentage of children who are tuberculin-positive; but the effects of declining infection are not confined to this group. It is reasonable to believe that in all groups of the community there has been a similar reduction in opportunities for infection. There is too a cumulative effect of declining rates—as fewer cases arise and die, so there are fewer sources of infection and fewer are infected. Improved case-finding programmes, isolation of cases, and the training of patients in hygienic disposal of sputum, have all helped to diminish the opportunities for dissemination of infection.

[1] See Crofton, p. 125 of this number of the Bulletin.—ED.

b. Improving Social Conditions

The association between adverse conditions of life and tuberculosis is well recognized. So far as mortality is concerned in Britain the association is clearly shown by the Registrar-General's decennial supplements, where tuberculosis mortality is regularly lowest in professional workers and highest in unskilled workers. It is likewise generally agreed that living conditions have greatly improved in the past century, and it is natural to regard this improvement as being the main cause of the decline in mortality. The work of Hart & Payling Wright (1939) lends strong support to this view, showing not only that improved environmental conditions accompanied the fall in tuberculosis mortality, but also that a check to the improvement in living conditions was accompanied by an arrest of decline of tuberculosis mortality in young adults. Improved housing, with reductions in the number and closeness of contact with infectious cases, forms one important element in improving social conditions. Using data based on the 1931 census in London boroughs, Benjamin (1953) was unable to separate housing as a factor from certain other adverse indices of feeding and occupational risk—the correlation between the various adverse features was too high to enable any one to be picked out as of special importance. On the other hand, using more recent data for smaller localities in Edinburgh, Stein (1952) showed that adverse housing conditions are a factor of importance when other circumstances have been allowed for. In this connexion, however, it is important to remember that housing in some Scottish towns is very bad indeed, and the influence of crowding as a separate factor may be identifiable only under such conditions.

c. Medical Measures

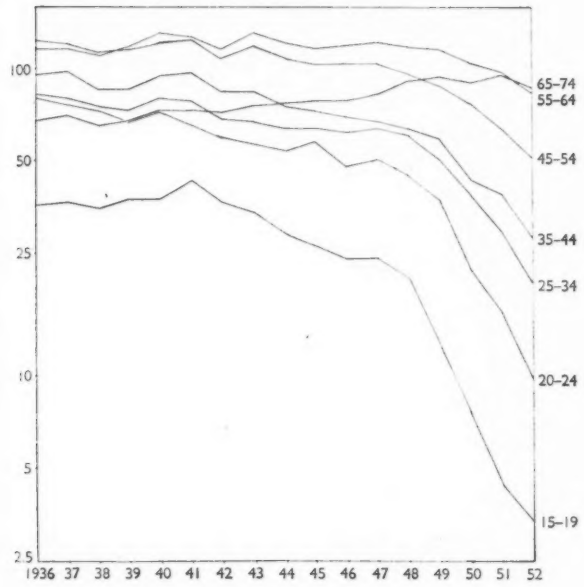
Treatment of the established case can have played little part in causing the decline of mortality that was recorded in some countries in the last century, and probably played only a very small part in the first half of this century. Sanatorium and collapse measures saved the lives of some, but probably had insufficient effect to be detectable in nation-wide statistics.

The marked decline in mortality, which first appeared in 1949 and which continues at the present time, coincides with the introduction of streptomycin, which was available in 30 institutions in England and Wales in July 1948, in 220 in April 1949, and was generally available on prescription from 1 November 1949. Hedvall & Hillerdal (1952) have noted that the recent decline in mortality in Sweden has benefited especially the younger age-groups. Figures 2 and 3 show that the same is true for both sexes in England and Wales. The recent sharp decline in mortality would appear to be due to effective treatment of cases of tuberculosis; the absence of any corresponding decline in notification rates lends some support to this view.

3. Sex Differences in Mortality

In every European country for which the World Health Organization recently published statistics (World Health

FIG. 2. MORTALITY FROM TUBERCULOSIS OF THE RESPIRATORY SYSTEM IN MALES, ACCORDING TO AGE, IN ENGLAND AND WALES 1936–52



Abscissae: calendar year
Ordinates: death-rate per 100,000 (logarithmic scale)
Age-groups (years) are shown at right-hand margin of graph.

Organization, 1953), more males than females die of tuberculosis despite a constantly greater female mortality in adolescence and young adult life. The mortality experience of both sexes is nevertheless similar up to the age of 25 years and the male excess is entirely accounted for by higher death-rates over that age. Graphs representing age-specific mortality rates vary considerably from country to country but it is generally true that the curve for females rises sharply in the 10–14 year age-group, from the low levels of childhood to a peak in the 20–24 or 25–29 age-group and then falls away, sometimes to rise again over the age of 60 years. The curve for males, on the other hand, tends to rise later and more gradually but continues to ascend until about the age of 60 years, after which it usually falls.

In the past when death-rates were higher at all ages in both sexes, male and female crude death-rates were less different than they are today. In England and Wales in the decade 1851–60 slightly more females died than males, the standardized mortality per million being 3,483 and 3,477 respectively. Though all age and sex groups have benefited from the falling rates they have not done so equally and in general older men have fared less favourably than older women. In both sexes there have been changes in the age at which the mortality is highest, but there are unfortunately very few countries for which reliable age-specific death-rates are available for a sufficient number of years to observe whether the changes are following any constant trend. In the 1860's the peak mortality for males in England and Wales was in the 25–34 year age-group and it has since moved steadily to its present position in the 65–74 age-group (fig. 4). The peak mortality for females, also in the 25–34 age-group in the 1860's, moved to the 35–44 age-group at the turn of the century and after moving slowly back in the other direction to the 15–24 age-group has now returned to the 25–34 age-group.

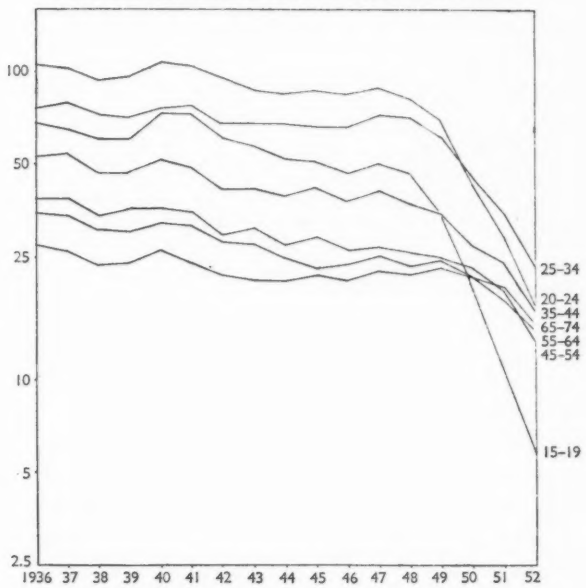
Similar movements have been noted in Scotland but not in Norway (fig. 5), Sweden or Ireland, where until 1940 young adults of both sexes had always experienced the highest death-rates. More recent figures for these three countries show an improvement in the mortality of young adult males, and men over the age of 50 years now have the highest rates.

In Scotland the recorded tuberculosis mortality began to decline later than in England and Wales, but a similar shift of the peak rate occurred in the rates for males. In young females in Scotland the rates were falling fairly rapidly in the early years of the century at a time when the rates for similar groups in England and Wales were falling little: even the First World War caused only a temporary increase in rates in Scotland, and the decline was renewed after that war. During the 1930's, however, little improvement occurred in the tuberculosis mortality of young adults in Scotland; there was a steep rise in rates during the Second World War, and the rates continued at a high level and even increased up to 1948.

4. Discussion of the Changes in Distribution by Sex and Age

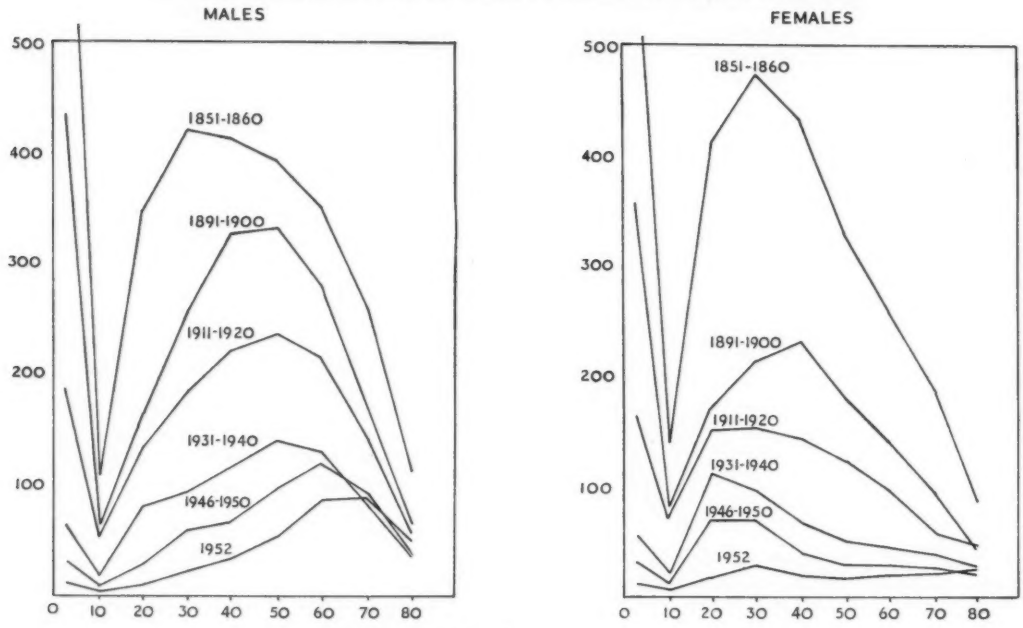
The interpretation of these observations is very difficult. The great importance of environmental factors in determining risk of infection and its eventual outcome is not doubted, but a person's environment immediately before death may be very

FIG. 3. MORTALITY FROM TUBERCULOSIS OF THE RESPIRATORY SYSTEM IN FEMALES, ACCORDING TO AGE, IN ENGLAND AND WALES 1936–52



Abscissae: calendar year
Ordinates: death-rate per 100,000 (logarithmic scale)
Age-groups (years) are shown at right-hand margin of graph.

FIG. 4. MEAN ANNUAL MORTALITY FROM ALL FORMS OF TUBERCULOSIS IN ENGLAND AND WALES, AT VARIOUS AGES, IN SELECTED PERIODS 1851–1952



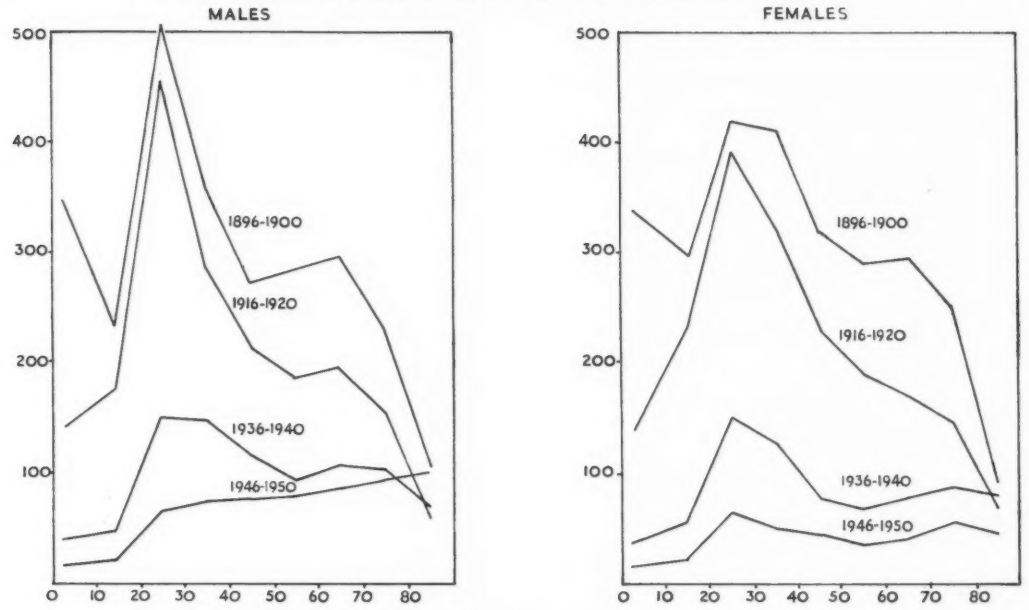
Abscissae: age (years)
Ordinates: mean annual mortality per 100,000

different from the conditions he experienced during the earlier years of life. Death from tuberculosis may occur a few weeks or many years after infection, and though recent events may be important, past events may be more so. A study of death-rates year by year shows that with few exceptions the mortality of males and females in all age-groups is falling, and it has been stated that this is probably due to improved living conditions. It follows that persons aged 50, for example, were subjected to the hazards of an adverse environment for 20 years longer than persons aged 30 and a comparison of their death-rates from a chronic disease in the hope of evaluating contemporary circumstances may prove misleading. The change in the pattern of male mortality observed in England and Wales since 1860 may indicate that the environment is now more favourable for young men than for older men or it may mean that older men are still suffering from the influence of the environment of their youth which later generations have not experienced. It is of course possible that both mechanisms have been at work.

Another method of studying mortality rates, usually known as the " cohort " or " generation " method, was introduced to attack this problem. The method was first applied to tuberculosis by Andvord (1930) and subsequently by Frost (1939), Picken (1940), Moine & Oudet (1947), Lancaster (1950), Daw (1950) and Springett (1950). In this method a cohort, that is, those born within a stated period of years, is followed until no survivors remain, and the tuberculosis death-rates are calculated at different ages. Studies of this kind have all shown that the curves representing the age distribution of deaths in cohorts are remarkably similar in shape and show no shift of peak mortality to older age-groups. Though this may encourage us to take a less serious view of the changing shape of the male mortality curve, it is difficult to understand firstly, why changes in the age incidence of tuberculosis mortality in females have been absent or transitory and secondly, why the over-all male mortality is so much higher in spite of an apparently greater female susceptibility in adolescence.

It was shown by Springett (1950) that for purely mathematical reasons the peak rate of mortality shifts to an older age-group more readily when the curve is rounded or plateau in type than when sharply peaked. It is certainly true for England and Wales that when the tuberculosis death-rates began to fall during the second half of the nineteenth century, the male curve was of the former and the female of the latter type. It is therefore more probable that a shift to an older age-group would be observed subsequently for males than for females. As the high mortality rates of the past would continue to reflect themselves for longer in male than female rates, a higher death-rate for older males would eventually, and for a limited period of time, be expected, though whether the difference would be of its present order is open to question. It is relevant to this discussion that it was found, in a study of repeat mass radiography examinations (Springett, 1951), that the highest incidence of new lesions was in young adults of both sexes, and as age increased the incidence fell steadily. If this observation is generally true, it must mean either that the paradoxically high death-rates in older males are due to the breakdown of long-standing lesions or that new lesions in older males have a bad prognosis.

FIG. 5. MEAN ANNUAL MORTALITY FROM ALL FORMS OF TUBERCULOSIS IN NORWAY, AT VARIOUS AGES, IN SELECTED QUINQUENNIA 1896–1950



Abscissae: age (years)
Ordinates: mean annual mortality per 100,000

We are left with the problem of assessing the extent to which environmental factors during middle and late adult life, as opposed to those during childhood and youth, influence tuberculosis mortality. Men and women are not exposed to identical environmental conditions and this may account in part for present sex differences in mortality. An attempt was made by Russell (1952) to disentangle past and present factors so far as young women were concerned. He concluded that phthisis mortality of young adult females aged 15 and aged 20 years was related to childhood environment, whereas beyond the age of 25 years the significant association was with contemporary environment.

It was noted by Dahlberg (1949) and McDonald (1952) that male and female mortality patterns are most alike under rural and least alike under urban conditions. The factor responsible for the difference is usually thought to be associated with employment, as to most other hazards of our cities men and women are exposed equally. The danger could lie in the increased risk of exposure to infection through close contact with large numbers of persons over long periods or perhaps in some factor as yet undefined, which increases the risk of breakdown of quiescent lesions.

The cohort method of analysis supports the belief that part at least of the present high death-rate of older men is the result of past conditions no longer operating. For this reason alone we may expect that there will be an improvement in the death-rates of older males during the next 10 to 20 years. However, there is evidence that the course of tuberculosis is also influenced by present events and there is at least a suspicion that part of the excess of male mortality is due to urban occupational factors. Considerably more investigation of these factors is required before the present number and age distribution of male deaths from tuberculosis can be attributed solely to a statistical artifact.

ACKNOWLEDGEMENTS

Figure 1 is based upon statistics published by the League of Nations Health Organisation and by the World Health Organization. Figures 2, 3, 4 and 5 are based upon rates derived from the published official statistics of Norway and from the Registrar-General's statistical reviews of England and Wales.

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THE DEVELOPMENT AND FUNCTION OF THE CHEST CLINIC IN THE CONTROL OF TUBERCULOSIS

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1 Origin of the tuberculosis dispensary
2 Growth of the chest clinic
3 Tuberculin testing
4 Functions of the chest clinic
  a Location
  b Diagnosis and assessment
  c The symptomless patient
  d Treatment and domiciliary care
  e Prevention of tuberculosis
5 The National Health Service Act of 1946 and the chest clinic
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1. Origin of the Tuberculosis Dispensary

In 1882, when Koch presented his final and definitive proof of the bacterial origin of tuberculosis, this disease was an outstanding cause of invalidism and death throughout the world. Chest hospitals in London and a few other centres already had out-patient departments attended by many tuberculous patients. Out-patient dispensaries, usually connected with a hospital, began to be established in other cities with the purposes of diagnosis and treatment. In 1887 the late Sir Robert Philip founded the Victoria Dispensary for Consumption in Edinburgh, planned with the aims of diagnosis, treatment and prevention. The scheme was comprehensive and included a room for laryngoscopy and a laboratory. A paid medical officer had the duty of supervising the treatment of patients in their homes. Removal of the patient to hospital, and disinfection of houses after death, were arranged in co-operation with the city authorities. A new feature was the provision of a nurse trained " in modern open-air methods " who visited homes and gave advice to the patient and the relatives on treatment and prevention. The work of Philip in Edinburgh (Philip, 1906) and the parallel activities of Calmette in Lille (Newsholme, 1908) became models for the dispensaries which were to appear in every centre of population. Philip's original papers had a wealth of detail; emphasis was placed on the chest hospital, the home for advanced cases and the convalescent colony, all regarded as vital parts of the scheme of prevention. At that time German workers favoured the sanatorium as a means of prevention, while French workers placed their faith in the dispensary and regarded the sanatorium as of curative value only. It was widely believed until recent years that sanatoria favoured the spread of tuberculosis by keeping alive the carriers of infection. Philip's conception of the dispensary was that of a centre in which every useful activity was co-ordinated. The family doctor, the sick person at home and the hospital or sanatorium all played a part in the scheme. The first dispensaries in England under the control of the local authority were established in Paddington and in St Marylebone, London, in 1909 and 1910 (Roberts, 1952). The National Insurance Act of 1911 provided sanatorium benefit, and in 1912 all forms of tuberculosis became notifiable. In 1913, another Act (Public Health (Prevention and Treatment of Disease) Act, 1913) made local authorities responsible for providing facilities for diagnosis and treatment and soon a great number of dispensaries were established. The service developed steadily between 1913 and 1939, within the limitations imposed by existing medical knowledge and the technical resources available. The larger centres, with certain notable exceptions, suffered from the separation of clinic and hospital work. In general, there was more progress in clinical medicine and in the all-important matter of rehabilitation in the sanatorium than in the dispensary.

2. Growth of the Chest Clinic

In the twentieth century important aids to diagnosis became available: radiography, fluoroscopy, miniature radiography and tomography extended the scope of physical examination; methods of blood examination, such as the Arneth count and later the erythrocyte sedimentation measurement, were introduced; aids to bacteriological diagnosis, which is the most certain and satisfactory proof of the nature and activity of a tuberculous lesion, have included cultural, concentration and microcultural methods. Indeed the variety of diagnostic aids has increased so much that the selection of a few tests of proved worth for routine use is imperative, in the interests of efficiency and of economy. The evolution of the modern chest clinic was hastened by the need to limit the number of centres, for efficiency in staff and equipment. Although the tuberculosis dispensaries, from which chest clinics have evolved, provided a service which was open to all, it was at first regarded as mainly for those who could not afford to pay for private medical care. The conception of a comprehensive clinic service, which gives the entire community the fullest resources for diagnosis, treatment and prevention, has evolved from the first dispensaries. The principles laid down by Philip—and later spread widely by his pupils—have exerted an immense influence on the tuberculosis service, particularly in the sphere of prevention.

Tuberculosis mortality in the British Isles had begun to fall before the discovery of the tubercle bacillus. This fall was interrupted during the First World War, and the Second World War again provoked a sharp rise in the tuberculosis death-rate. Two important measures of prevention resulted: mass miniature radiographic surveys of personnel of the armed forces and of industrial workers, and the provision of special monetary allowances to encourage the patient with pulmonary tuberculosis to stop work. These allowances, described in a memorandum by the Ministry of Health (1943), proved highly effective in raising the demand for treatment. Experience has proved conclusively that workers will not give up their employment on account of early tuberculosis, unless there is reasonable financial provision. One result of mass radiographic surveys was a great increase in the number of what are known as " observation cases ", symptomless and

often normal in aspect, but with signs of a tuberculous lesion. In another important group signs indicative of non-tuberculous disease were disclosed. Apart from mass surveys, the use of chest radiology increased enormously between 1940 and 1950, in tuberculosis clinics, in general hospitals and in industrial and private practice.

The introduction of a scheme for *x* raying the chest without medical examination, available after working hours at the request of the patient's doctor, proved successful in two London boroughs (Toussaint & Pritchard, 1944). As a result of these developments and also because of the brilliant therapeutic results of antibiotic treatment and of thoracic surgery, the relation between tuberculosis mortality and known tuberculosis morbidity has changed. In England and Wales, deaths from respiratory tuberculosis fell from 25,259 annually in the period 1931–39 to 12,031 in 1951. The number of new respiratory cases, as shown by notification returns, rose from 37,879 in 1938 to 42,415 in 1950. The number of respiratory cases on chest clinic registers in 1951 was 250,889, as compared with 138,483 in 1938. The death-rate for respiratory tuberculosis has fallen and is still falling, the number of new cases has increased slightly and the total number of known cases has almost doubled since 1938. Chest clinics in England and Wales have now responsibility for the clinical supervision of a quarter of a million patients as well as of a large number of observation cases and "contacts", that is, persons who are known to have been in contact with the disease.

3. Tuberculin Testing

Koch introduced tuberculin in 1890 but the subcutaneous diagnostic test, which was first employed, proved clumsy, unreliable and not entirely free from danger. In 1907 the cutaneous test of von Pirquet and a year later the intradermal test of Mantoux provided safe and simple methods of ascertaining the fact of previous infection. The early results of tuberculin testing, based on the observation of hospital patients and primary-school children in cities, indicated that infection by the tubercle bacillus was almost universal before the fifteenth year. It appeared that the test would be of diagnostic value only in young children. Subsequent work, extended to wider social groups and to suburban and rural areas, showed that infection-rates varied widely and that many persons escaped infection until adolescence or early adult life. However, the first impression of the universality of infection, which was supported by the post-mortem findings of Parrot (1876), Naegeli (1900) and Ghon (1912), was for a considerable time widely believed to be correct. After the First World War several serial observations were published in Scandinavia and North America, which showed that infection-rates in all age-groups up to 16–20 years had fallen dramatically, as a result of the campaign against the tubercle bacillus. For example, Ustvedt (1942) found that the percentage of children who gave a positive reaction to the Pirquet test in Trondheim, Norway, had fallen between 1914 and 1930 from 24 to 8 at 8 years and from 60.5 to 40.5 at 15 years. The comprehensive monograph of Hart (1932) provided a complete picture of the world position up to 1930. Since then, and particularly in the last decade, infection-rates have continued to fall. A very complete picture of the extent of infection in Great Britain in 1949–50 has been provided by the National Tuberculin Survey (Medical Research Council, 1952). While there are rather wide differences between rural, urban and mining areas, the results show that more than half the population have escaped infection at school-leaving age. In many communities infection at school-leaving age is the exception, rather than the rule. The tuberculin test, particularly in children and young adults, is now an indispensable diagnostic procedure and has an important place in the work of the chest clinic.

4. Functions of the Chest Clinic

Common sense dictates that the service must first meet the urgent needs of the community. Where staff and equipment are limited, the routine use of tuberculin testing, chest radiography—even by a miniature method, if necessary—and the application of a standard bacteriological test permit large numbers to be examined and assessed quickly. If hospital beds and out-patient facilities are lacking the clinic must provide treatment sessions and arrange for domiciliary treatment. Prevention, using the term in a wide sense to include diagnosis and the application of case-finding methods, should take first place. Many aspects of treatment have become so technical since the days of Sir Robert Philip that, in the interests of the patient, they should be effected in the wards or out-patient departments of tuberculosis hospitals. Supervision of home treatment and regular attention to the economic and social needs of the tuberculous patient and his family are an important part of the work of the clinic.

a. Location

In rural districts and in areas of low population density, the clinic should be in a general hospital, with the other out-patient departments. This is liked by patients, facilitates consultations with other specialists and brings the chest physician near to the wards, where he finds many new cases. Cities need a whole-time clinic, planned for day and evening clinical and "contact" sessions, and with ample accommodation for administrative and clerical staff.

b. Diagnosis and Assessment

The basic needs are a keen medical staff, adequate time for investigation of the difficult case, a high standard of radiography (including tomography) and a good laboratory service. It is probably an extreme view that tuberculosis should not be diagnosed in the absence of a positive bacteriological or pathological finding but undoubtedly the number of errors in diagnosis will vary inversely in proportion to the efficiency of the laboratory services and the zeal with which material is collected. Full use should be made of culture of sputum, gastric juice from the fasting patient, and the laryngeal swab.

c. The Symptomless Patient

Mass radiography, examination of contacts and other case-finding procedures have brought to notice many tuberculous lesions of varying significance. The co-operation of the patient is encouraged by rapid and thorough examination, by complete frankness and by night clinic appointments.

In doubtful cases, the patient should not be urged to stop work but the intervals between appointments must be short (four to six weeks). The chest clinic, which has the confidence of local practitioners, attracts a variety of forms of intrathoracic disease, the investigation of which requires

radiography of a high standard. A small number of beds for persons requiring observation is indispensable. Every chest hospital should have at least one male and one female ward for patients in whom examination for tubercle bacilli has proved negative. A number of observations of non-tuberculous disease from chest clinics has been published recently. Wynn-Williams (1953) has described the radiological appearances of undiagnosed bronchiectasis, and Mackenzie (1953) has assessed the incidence of bronchiectasis in the Leicester area. Chronic bronchitis is seen daily in the chest clinic, with or without active tuberculosis. In the future, investigation and treatment of this common, disabling disease may be a valuable part of clinic work. The early detection of bronchial carcinoma is another important responsibility.

d. Treatment and Domiciliary Care

Specialized techniques, and particularly collapse measures, have shown the best results when performed in chest hospitals and continued in the out-patient department (Clarke, 1948). However, lack of beds may necessitate the execution of such treatment in the clinic or in the home (Clarke, 1952). Good results have been reported by Heller (1947), Maclean & Gemmill (1948), Tattersall (1949), Trenchard (1949), Wynn-Williams, Shaw & Mashiter (1950) and Toussaint (1950). Success depends on the selection of cases and organization of a team with sufficient time to give close attention to the patient. Clinical supervision of the domiciliary case is a relatively neglected aspect of tuberculosis work, which has an important bearing on prevention. A high standard of hospital care is now general but more help should be afforded to the tuberculous patient in his home. When the chronic phthisical patient realizes that nothing more is to be done to help him, he tends to disappear and finally his name is removed from the register. The staff of the clinic should include a good almoner, and a home-nursing service should be available to supplement the excellent work of the health visitor. In this way the needs of the chronic patient, and particularly the housing question, will be brought constantly before the clinic physician. All cities require hostels and small labour-saving flats for the chronic tuberculous who are homeless or unsuitably housed. Apart from humanitarian considerations, this provision helps to prevent the patient from descending to the lowest rung of the social ladder and so spreading infection in common lodging houses. A " meals on wheels " service, providing one hot meal daily for the chronic patient who lives alone, would be useful, and a dietician with practical knowledge of home cooking could do much good.

e. Prevention of Tuberculosis

Prevention is the true aim of the clinic service. It is dependent on medical, nursing and technical skill but, to be effective, must go beyond the clinical care of the patient.

i. *Organization.* Gaps in notification, patients not recalled at the proper time, patients lost sight of and an insufficient number of contacts examined point to flaws in the system. Such failure is essentially due to deficiency of properly trained and selected staff and to antediluvian methods of records and filing. No industrial concern would attempt a task of the magnitude of the clinic and home supervision of more than 250,000 people, with the resources at the disposal of the present service.

ii. *Contacts.* The search for tuberculosis in contacts should be followed by measures to protect the tuberculin-negative contact from infection and to raise the resistance of the apparently healthy, positive reactor. Removal of the known source of infection, search for other sources of infection in the home, attention to diet and the placing of delicate or undernourished children in open-air day or residential schools are important. Contacts of school age should attend a special session—Saturday morning is the convenient time—for examination, *x* ray and a tuberculin jelly test. They can return to an afternoon clinic for reading of the test three to four days later. If the tuberculin test is negative and clinical and *x*-ray findings are normal, all contacts should have the protection of *Bacille Calmette Guérin* (BCG) vaccination after six weeks' separation from the source of infection. Infant contacts require two afternoon sessions weekly, for reading of tuberculin tests. Children should on no account be mixed with adult patients. Unless there are two entrances and two *x*-ray departments in the clinic, they should have separate sessions. Adult contacts should be called to evening sessions. BCG vaccination is an important protection also for the adult contact who has escaped infection. Many prove negative to the initial Mantoux test, even those who are contacts of open cases (Grenville-Mathers & Trenchard, 1953). Miniature radiography at night sessions is valuable for the re-examinations of healthy contacts but the observation of doubtful lesions demands full-size films.

iii. *Examination of suspects.* The *x*-ray examination of patients referred by their doctor on account of vague symptoms has proved so successful that it is now general. One night clinic weekly should be set aside for this work, unless it is arranged at the local mass radiography centre.

iv. *BCG.* Child and adult contacts can have their vaccination and post-vaccinal tests at the contact sessions held for them. It is most important not to mix them with clinic patients during these visits. Hospital workers, medical and dental students and the other groups selected for vaccination are best kept away from the chest clinic. Testing and vaccination can be arranged in their school or place of employment. In the writer's opinion, BCG vaccination should be advised for children leaving school and young industrial workers who are negative to the Mantoux test, until the pool of infection in the community has diminished.

v. *Control of infection in the home.* When a fresh case of tuberculosis arises, the health visitor's report on the home conditions and family will show the doctor whether an almoner's help is needed. It is the responsibility of the clinic physician to secure the co-operation and interest of the general practitioner. Sputum flasks or mugs, disinfectant and paper handkerchiefs should be issued free when there is financial need. The loan of bed and bedding is accepted so frequently as to emphasize the extent of poverty and overcrowding among the tuberculous. The minimum standard of housing to be tolerated should provide a separate room for the person with active phthisis who has to be nursed at home. The 250,000 patients on clinic registers include a relatively small number of chronic, semi-ambulatory or bed-fast subjects in their homes. The protection of their attendants and contacts in the home should be of the same standard as that afforded to the tuberculosis nurse: at the least, overalls should be provided. If the sick-room is well ventilated, the main source of infection lies in the bacilli deposited on the clothing and bed-covering of the patient and stirred into the air again by bed-making

and other activities. A laundry and disinfecting service for clothing, bedding and also for the overalls of the attendant would diminish an important source of infection. These services are provided without question in chest hospitals and that they are not available for the domiciliary patient merely proves that preventive measures are valued low in certain quarters. Soap and water, applied to the person, to clothing and to the floor-coverings and furniture, are the best of all disinfectants against the tubercle bacillus. A home-nursing service and the provision of domestic help are of great value in domiciliary care.

vi. *Education.* A recent public opinion survey in London (Gore & Hartston, 1953) showed that many young married women had misconceptions about tuberculosis; almost half of those questioned thought the disease was hereditary and 21% were ignorant of the danger of contagion. But the same survey showed that fear of tuberculosis tended to prevent the attendance of contacts and others at chest clinics. Methods of education or of propaganda that arouse fear or anxiety are likely to defeat their object, by creating unconscious resistance to action against tuberculosis; and facile optimism is equally futile. The distribution of simple literature, so worded as to stress the value of positive health measures and of mass miniature radiography and BCG, is worth while. Other publicity, which must be strictly factual, should be directed to potentially interested and influential groups, such as politicians, employers and trade-union organizations, civil service and public authority officials, teachers and social workers.

vii. *Rehabilitation* is mainly the concern of the Ministry of Labour and National Insurance in Great Britain and in Northern Ireland, but the chest clinic service has a responsibility. The ideal of complete restoration of working capacity is often achieved but many patients become fit only for sheltered employment (Hardy, 1953). The challenge of this important but difficult problem has been faced already in some areas.

5. The National Health Service Act of 1946 and the Chest Clinic

This Act made revolutionary changes. The tuberculosis officer became a chest physician and was placed on the same footing as other medical specialists. Clinic duties were combined with consultant supervision of hospital beds, and a proportion of working hours (three-elevenths) was allotted to preventive work. Mass radiography and BCG vaccination were placed under the control of regional hospital boards. The medical officer of health was relieved of most of his responsibilities regarding tuberculosis. The chest physician ceased to be under his control, although provision was made for consultation. Notification, a well-defined legal responsibility of the doctor, was formerly supervised by the medical officer of health but the new position under the Act is not clearly defined. Prevention and after-care remain in the sphere of the local authority. Important improvements have resulted from these changes. The standards of investigation and diagnosis have been stimulated, to the benefit of the patient. The new establishment offers a career in clinical medicine to the able and energetic student of respiratory disease. The opportunities of combining hospital and clinic work should inculcate a balanced view of tuberculosis problems.

On the other hand, the medical officer of health is a specialist in preventive medicine, with administrative experience and control of a trained administrative staff. Notification in some areas is less efficient now than before July 1948. The Chief Medical Officer of the Ministry of Health has pointed out that " one death from tuberculosis in every six occurs in persons not notified before death " (Ministry of Health, 1952). The percentage of such unnotified deaths rose from 12 in 1939 to 17 in 1950 and the increase affected both respiratory and non-respiratory cases. Deaths from non-notified respiratory tuberculosis rose from 1,867 in 1938 to 2,600 in 1949 but fell to 2,067 in 1951. Owing to the fall in the total of tuberculosis deaths, the percentage increase exceeds the numerical increase. Cox & Hughes (1953) consider that this rise is likely to impair the effectiveness of tuberculosis control. Information concerning the age of the non-notified fatal cases would be of interest, as they may consist largely of older, chronic cases. The best way to ensure complete notification is to offer something of value to the older patients whose names tend to disappear from the clinic register. They do not need long periods in hospital but often have no satisfactory alternative to the shelter of an institution. Their best hope of a quiet life may lie in the concealment of their disease, the disclosure of which makes it hard for them to find a place to live.

The Regional Hospital Board is less democratic than the local authority which it superseded and this may promote efficiency on the short-term view. But it may be asked whether the Boards will understand local conditions and ways, whether they will show enthusiasm for new ideas and, if so, whether they can overcome the inertia of their monolithic administrative structure. The ever-increasing cost of health services will soon result in a call for economy (Banks, 1952). The new service will be judged by the success or failure of efforts to reduce morbidity and incapacity for work. It is encouraging that the 1951 Report of the Chief Medical Officer of the Ministry of Health (Ministry of Health, 1953) shows a fall in the number of new cases, following a steady increase since 1938. This is encouraging, for a decline in the number of new cases is an index of the effectiveness of preventive efforts.

The control of tuberculosis depends on many factors, not all of which are within the sphere of the clinic service. Maintenance of a good standard of life and the provision of more beds, particularly for the older patients who are carriers of infection, are important aims. It is for the chest clinic to direct and execute every measure of prevention that promises to reduce the number of new cases of tuberculosis.

6. Summary

The tuberculosis dispensary has evolved from the hospital out-patient department, under the influence of the conception of prevention taught by Sir Robert Philip and his pupils. The growth of the chest clinic resulted from the scientific and technical advances that have occurred since the discovery of the tubercle bacillus in 1882. Tuberculin testing has come to assume cardinal importance, both in the clinical field and in epidemiological studies. The functions of the chest clinic have been described under the headings of diagnosis, treatment and domiciliary care and prevention. The changes made by the National Health Service Act of 1946 have been discussed. The success of clinic work is now to be judged by the control of morbidity from tuberculosis.

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PROBLEM OF THE TUBERCULOUS PATIENT IN INDUSTRY

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1 Tuberculosis : a special chronic illness
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References

The four main divisions of medical practice are prevention, diagnosis, treatment and rehabilitation. In tuberculosis the two latter go together, since treatment is not complete until the patient is once again able to earn his living and support his family.

1. Tuberculosis: a Special Chronic Illness

In Great Britain attention was focused on the special problems of the tuberculous patient during the man-power shortage of the war years by the issue of a memorandum by the Ministry of Health in 1943. This provided special measures of financial assistance for sufferers from respiratory tuberculosis, to encourage diagnosis and treatment at the earliest possible stage, with the twin objects of care of the individual and removal of sources of infection. The payments made to those who gave up remunerative employment to undertake treatment consisted of a standard rate of maintenance, and additional payments (after need had been established) towards meeting exceptional commitments such as high rent, education, insurance, hire-purchase payments, and so forth. These payments were a recognition that tuberculosis is a special chronic illness, and they are now largely continued under the National Assistance Act, 1946. Further recognition of the special position of tuberculosis has been the scheduling of the disease under the National Insurance (Industrial Injuries) Act, 1946. Under this Act anyone who develops tuberculosis while in certain employments, such as nursing or health visiting, receives benefits which are in general higher than the corresponding benefits under the ordinary National Insurance Scheme.

2. Analysis of a Male-Employment Register

Analysis of the register at Harrow Chest Clinic, which serves a population of approximately a quarter of a million (a great number of whom work up to 10 miles away in central London), shows that there are at present (January 1954) 723 males with pulmonary tuberculosis who were over 15 years of age at the time of diagnosis and are below the retiring age of 65. Cases of pleural effusion have been excluded, since this type of tuberculosis falls into a special category. Only male patients have been considered, since with women the time of return to employment is difficult to define, especially in the case of housewives, and since so many women do not return to employment after treatment. Of the 723 men, 140 (or 19%) are a purely medical problem, comprising newly diagnosed cases, those who have relapsed and are undergoing further treatment, and those who are chronic invalids; 519 (72%) are at work, and 64 (9%) constitute a social problem. The latter two groups are discussed separately.

3. Difficulties in Rehabilitation

Our first concern is with the large group who have returned to work. Once a patient has been discharged from a chest hospital and his specific treatment has been completed, he can be kept away from work too long. During treatment the patient spends a long time in bed at home and in hospital away from the rush and bustle of modern life. Such people frequently find that it is difficult to become adjusted once again to ordinary living conditions. Many are frightened to face life, try to make for themselves a small circle of interest, and are afraid to take the step of starting work again in the competition of open industry. Sometimes these people have almost to be forced back to work—but once they have returned they find their confidence returns.

A major cause of this reluctance to return to work is the fact that rehabilitation is considered too late in the patient's treatment. Occupational therapy is frequently the only effort made towards rehabilitation in chest hospitals. Although a good deal of energy is expended by occupational therapists on helping the tuberculous, and the diversional value of this work is high, it provides no lasting solution for the major problem which confronts these patients, and the gulf between occupational therapy and rehabilitation does not appear to be decreasing.

Non-manual workers can, and frequently do, take up correspondence courses, while undergoing treatment, to help them in their later work. The British Student Tuberculosis Foundation in conjunction with the North-West Metropolitan Regional Hospital Board have recently opened, for an experimental period, a student rehabilitation unit at Pinewood Hospital, Wokingham, Berkshire, where students can be admitted once they are up for four hours daily, with the object of continuing their studies while under medical supervision. For manual workers, unfortunately, graded walks seem to be the main method of rehabilitation. A system which would include increasing hours in some kind of workshop would give these people more confidence that, one day, they will be able again to earn their own living.

a. Requirements for Return to Work

To allow a patient to return to work, the first requirement is suitable living conditions and, if these are poor, efforts

should be made to improve them earlier whilst the patient is undergoing active treatment. Secondly, the job must be sufficiently remunerative for an adequate standard of living, and therefore a change of occupation for a tuberculous patient should, if possible, be avoided. Thirdly, it is important that there should be no long journeys from home to the place of work. Finally, the job itself must not be too strenuous or involve excessive hours of work, but it is preferable to have a heavier job near to the patient's home than a light job at a distance.

The most suitable job for the ambulant tuberculous patient is, therefore, usually the job he knows most about. Thus, of those who returned to work in 1952 in Harrow (Table I),

TABLE I. THE PLACING OF 87 MEN CERTIFIED FIT FOR WORK IN HARROW IN 1952

Age-groups (years)	Male patients fit for work in 1952		
	Not placed	Placed	
		Suitable	Unsuitable
15–29	3	44	—
30–39	2	14	2
40–49	—	8	1
50–59	—	11	—
60–64	—	1	—
Over 64	—	—	1
Total	5	78	4

85% took up their previous employment or some modification of it, and it has been found that previous employers will often offer modifications of working conditions if they are approached directly. Even in occupations which seem at first sight to be totally unsuitable for the tuberculous, such as dock work, many suitable jobs can often be found in the industry concerned (Grenville-Mathers, 1949).

b. Disabled Persons (Employment) Act, 1944

The return to previous employment has been helped by the provisions of the Disabled Persons (Employment) Act that was passed in 1944 to assist those handicapped by disablement to secure employment or to work on their own account. Patients who have suffered from tuberculosis are eligible for registration as disabled persons, and employers with more than 20 on their pay-roll are required to employ 3% of registered disabled persons. In addition, employment as an attendant in a lift or a car-park can now be undertaken only by disabled persons. There are some 850,000 registered disabled persons (Ministry of Labour, 1953b) of whom approximately 52,000 are suffering from pulmonary tuberculosis—6% of the total—so that most employers have, at some time, to consider the employment of persons suffering from tuberculosis, and they are usually pleased to fill their quota by taking on registered disabled persons with tuberculosis who have previously worked satisfactorily for them.

The institution of the Disabled Persons Register has been a help in getting patients back into industry, but its working could be improved. The Register appears to be swollen artificially by many who are not, in fact, substantially handicapped. Many are advised by their employers to register so that the firm's quota of disabled persons employed is reached. Careful scrutiny of application forms by a medical panel supplemented, if necessary, by medical examination is required, and substantial disablement should be a necessity for registration.

Difficult and arduous travelling, the heavy nature of the former job, or reluctance of the employer to reinstate a patient, call for a change of employment. To find this, application is made to a Disablement Resettlement Officer of the Ministry of Labour. This office was created by the Disabled Persons (Employment) Act (1944). Its function is to scrutinize all notifications of employment vacancies at the Labour Exchange, and to reserve those which appear suitable for the disabled persons on the Register. This Officer is also responsible for seeing that firms employ the full quota of disabled persons, and where this is not so to try and submit disabled persons for any future vacancies in that firm. He tries to maintain liaison with hospitals and clinics, so that he can learn which patients will soon be fit for employment. The placing of disabled persons is very much dependent upon the initiative and drive of the Disablement Resettlement Officers, who require intensive training for their posts. Not all Disablement Resettlement Officers have had the advantage of such training; and on the other hand enthusiastic Officers are often promoted and transferred as soon as they have become efficient at their job and aware of the problems in their own area.

When a tuberculous person becomes fit for work the Disablement Resettlement Officer is given a brief medical report on a special form, but this gives only a very limited idea of the capabilities of the patient. Attempts have been made to add to this information by reducing the assessment of the working capacity of the tuberculous patient to the exactitude of a laboratory report (Brieger, 1938, 1952). Such tests have not been found to constitute a better criterion for employment than a general assessment of the patient carried out by the physician who has treated him and who knows his clinical, technical, and temperamental qualifications. Fitness for employment cannot be defined by physiological measurements alone, since all men are individuals.

The placing of tuberculous persons in new employment is facilitated by a meeting of the patient, physician, clinic welfare officer, and Disablement Resettlement Officer, at a resettlement conference (Geddes, 1952; Grout, 1952). Such a resettlement conference is of great value to the patient who is not sure of himself, since he realizes that an effort is being made to find him suitable employment, and it also has a salutary effect on the patient who has for the moment lost the impulse to work. The conference should also stimulate the Disablement Resettlement Officer, since inquiries can be made of him regarding patients who have already attended such a conference.

c. Industrial Rehabilitation Units and Government Training Centres

The Ministry of Labour provides Industrial Rehabilitation Units (Ministry of Labour, 1953a) for those who need to fit themselves for work after finishing hospital treatment. Only three Harrow patients have been to such a Unit. This was at a time when one was in operation near to the Clinic, and had it continued in operation it would probably have been used more extensively for those in whom loss of confidence is the only barrier to a return to effective work. At the present time

there is only one such Unit, and another is proposed, for the whole of what is called Greater London (population approximately eight million), with a total of 14 Units for the whole of Great Britain.

The Ministry of Labour also provides courses for those who need training to enable them to take up suitable employment. Training can be given in Government Training Centres, in private institutions and in employers' establishments. These courses can be of help to those young disabled persons who have done previously only heavy unskilled work or who have fallen ill shortly after leaving school. Training courses for the following occupations are in operation, and they lead to a semi-skilled status for the trainee : carpentry, wood-machining, coach-building, light leatherwork, typewriter mechanics, repairing of watches and clocks, retail tailoring, men's hairdressing, draughtsmanship, shorthand and typewriting, book-keeping and other commercial subjects. Such courses usually last six months. The training is free, and, in addition, learners are paid a weekly allowance to maintain themselves and their dependants during training, the allowance being just a little less than they would earn when in full employment.

In recommending a disabled person for training, care must be taken to ensure that suitable employment will be available in the area afterwards. Twenty-six of those on the male-employment register of the Harrow Chest Clinic have been on training courses, the most suitable of which have been in shorthand and typewriting, commercial subjects, draughtsmanship, bench carpentry, and the repairing of watches and clocks.

At the present time there are only four Government Training Centres in the London area and 19 in Great Britain as a whole (Select Committee on Estimates, 1951). This means that a great number of patients have long distances to travel to these Centres and there are no facilities for part-time training, nor can training commence with shortened hours. Patients can live in lodgings near the Training Centres, and they are given an allowance to pay for these lodgings, but most applicants are unwilling to prolong further the separation from their families after a long period of treatment. More use would be made of these training courses if the present rigid rules could be relaxed.

4. The Tuberculous, as Worker

From the employer's point of view the tuberculous worker is a reliable worker with a sickness rate similar to the general sickness rate for the whole of England and Wales (Clarke, 1953). On the current register of male patients of the Harrow Chest Clinic, there are only five classed as definite malingerers, and O'Malley (personal communication, 1952) found, on analysing the records of 100 disabled unemployed persons registered with the Labour Exchanges, that none with tuberculosis was in the permanently unemployable group.

Further evidence comes from an analysis of the employment records of 570 men with pulmonary tuberculosis (excluding pleural effusions) at Harrow who have worked at any time since diagnosis, the results being calculated in life-table form. Of these, 198 had a negative sputum when first diagnosed and 372 had a positive sputum. Both groups have been subdivided at the age of 40, since employers discriminate between people under and over this age, and this also fits in with the two main peaks of incidence of tuberculosis in the male population (Anderson, Grenville-Mathers & Trenchard, 1951). Relapse has been classed as any incident in the disease causing relinquishment of employment for any period exceeding three days, and therefore includes not only reactivation of disease or fresh involvement of another part of the lung, but also such occurrences as admission to hospital for aspiration of pleural fluid. The employer is concerned with absence from work rather than its cause. The calculation of a life-table based on these criteria shows the percentages of males in continuous employment at the end of three and five years (Table II). This table is based on 56% of the original total at three years and 32% at five years.

TABLE II. PERCENTAGE OF MALES IN CONTINUOUS EMPLOYMENT AT THE END OF THREE AND FIVE YEARS AFTER THEY HAD BEEN PLACED IN EMPLOYMENT

Period	Sputum always negative (%)		Sputum at some time positive (%)	
	Age-group 15–39	Age-group 40–64	Age-group 15–39	Age-group 40–64
End of 3 years .	82	93	77	77
End of 5 years .	79	87	71	70

These figures show that tuberculosis is not invariably a relapsing disease, once the patient has become fit to work again. It appears that there is, however, a minority who relapse; a second life-table constructed to show those who have once stopped work and returned again indicates that only 30% of these were in continuous employment at the end of five years.

There is very little difference in the percentage of patients still working between those who at first diagnosis had a negative sputum and those who had a positive sputum; this is probably related to the criteria adopted for notification. In the absence of positive bacteriological findings, patients have been taken on to the notification register only if radiographs in series showed a spreading lesion or if tomography demonstrated a cavity. Patients not fulfilling these criteria have been kept under observation but not regarded as cases of active tuberculosis. Cultures of sputum and laryngeal swabs have been used extensively as a help to determine activity of a lesion.

5. The Fit Patient with Positive Sputum: a Medico-Social Problem

The greatest problem in rehabilitation of the tuberculous is posed by those who are classed as constituting a medico-social problem (9% of the total male register). These men are fit to work full time and yet have a persistently or intermittently positive sputum—usually on culture.

Seventy-one men on the current employment register have returned to work with a positive sputum, 21 of them against advice, and it is interesting to note that in 12 men the sputum eventually became negative, while they continued at work. The work record of these 71 men was quite reasonable; a life-table shows that 48% were still in employment without relapse (as previously defined in section 4) at the end of five years. Some returned to their previous employment, but others found their own jobs, frequently by concealing their disability from the employer and the true nature of their work

from the chest physician. Up to 1952 the facilities of the Labour Exchanges were not fully open to these men and therefore few in this category were submitted to the Disablement Resettlement Officers, but the position has changed with the issue of a circular by the Ministry of Health (1952) which lays down (inter alia) that there need be no general bar to the placing of persons with open tuberculosis in ordinary employment, provided that the placing of the individual in the particular employment concerned is subject to medical guidance and approval. The circular recognizes that it is the unknown case of tuberculosis which is usually responsible for the spread of disease (cf. Aspin, 1952; Grenville-Mathers & Trenchard, 1953). The provisions of the circular might eventually be operated so as to discourage these people finding jobs by their own effort and without medical guidance, although so far the Disablement Resettlement Officers seem very reluctant to implement this circular, and Industrial Medical Officers have some misgivings (Grenville-Mathers, 1953).

a. Village Settlements

The village settlements have, in the past, been regarded as the ideal solution for this group of patients. However desirable such settlements may be in theory, advantage of them is taken by only a minute fraction of those for whom they are intended. Only two male patients from Harrow are in settlements. Even if the patient himself is willing to enter a colony the family are usually reluctant to leave their own district and friends. Studies made at the settlements have, however, dispelled some misconceptions by showing that no harm has come from admitting to ordinary employment patients with positive sputum, provided that they have satisfactory living accommodation and proper working conditions. The aim should be to apply this experience to those in their own homes by the provision of sheltered workshops for patients with positive sputum able to work at least six hours per day. For a population of half a million a workshop accommodating 75–100 men is required. Workshops based on such a population, if urban, would keep travelling to a minimum; this is essential, because a patient who is in need of sheltered employment also needs a short journey to reach his work.

b. Sheltered Workshops

Throughout Great Britain there are 92 sheltered workshops set up by Remploy Ltd., a company constituted under the Disabled Persons (Employment) Act, 1944, and seven of these are reserved for the tuberculous. Unfortunately these workshops are each based on too great a population, and this means tedious travelling for many workers. This company has a tendency to distrust mechanization and mass production methods, whereas sheltered workshops should if possible be more mechanized than open industry. In addition the most suitable industrial processes do not seem to have been always selected and the company appears to have concentrated at times on providing charitable employment regardless of cost. As a result the financial record of the company is not satisfactory and in 1952 the loss per disabled person employed was £380 per annum (Select Committee on Estimates, 1951). Where the criteria of selection of entrants have been strict, however, the work results have been good (Hardy, 1953) and the above objections should not apply to smaller "local" workshops if these are set up by the local health authorities. These authorities have powers to set up such workshops under the National Health Service Act, 1946, but so far they have been reluctant to use their powers. Yet local authorities themselves use a variety of goods that could be produced in such workshops. Such factories, employing mainly disabled persons, cannot be expected to make a profit but the deficits shown by the orthodox methods of book-keeping are balanced by the saving to the National Assistance Board, National Insurance Fund, and the Ministry of Pensions and National Insurance. These funds, in the absence of sheltered workshops, have to cover the costs of the worker's maintenance where the patient cannot find work in open industry or, having found unsuitable work, suffers a relapse in his disease. Such a scheme would also allow these unfortunate people to become, once again, productive members of society and to enjoy a higher standard of living with a better chance of keeping their disease under control and with their mental outlook improved by feeling themselves to be self-supporting.

The provision of such sheltered workshops would also provide centres from which to operate a home industry service for the home-bound disabled, who might be given some work as a kind of subcontract from the workshop.

6. Conclusion

From what has been said above, it can be seen that, although the rehabilitation of many patients who are recovering from tuberculosis can be effected fairly easily, there are for a substantial minority a number of difficulties, and these require the co-operation of employers, governmental agencies and their medical advisers. Given goodwill and satisfactory conditions, the majority of patients can, however, become productive members of the community. If the newly diagnosed patient can look forward to such a prospect this confidence is of the greatest help in encouraging him to submit to a tedious programme of treatment.

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THE DETECTION OF PULMONARY TUBERCULOSIS IN A COMMUNITY

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1 Community surveys
2 Factors influencing the success of surveys
3 Results of community surveys
4 Effects of such community surveys
5 Other diseases
6 Summary and conclusions
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The drive to detect cases of tuberculosis in the community stems from clinical, preventive and scientific medicine. The importance assigned to various aspects of tuberculosis work may sometimes differ, but all three types of worker are agreed about the final goal—the detection of all the cases. In the early part of this century, such a general approach to the subject was prevented by overwhelming technical difficulties. The lack of an accurate, cheap method of diagnosing pulmonary tuberculosis prevented large-scale surveys. At this stage the organization of the dispensary, where the sick were diagnosed and contacts examined, was the only step that could be taken. It was, and still is, a very effective technique—particularly when reinforced by modern *x*-ray diagnostic methods—but alone it can never detect all the cases.

A few decades later, an object lesson in the importance of detecting all the " cases " was given by the successful attack on bovine infection in the United States of America, but it was not until 1936 when de Abreu (1939) demonstrated the use of photofluorography for mass *x*-ray examinations of the chest that a suitable technique became available. Unfortunately, the war intervened and the new technique was, very reasonably, rushed into daily use, *x* raying recruits and factory workers, and there were no machines or research workers available to *x* ray complete communities. It was introduced as a therapy for the community, rather in the way that pneumothorax, but not streptomycin, was introduced as a therapy for the individual in Great Britain. It was given in various " doses " to various groups, and little effort was made to study the effect of the dose on the group. The result is that there is now in Great Britain a certain disillusionment about mass radiography, signalized by the " Whither mass radiography? " sort of article, and a lot of acrimonious discussion amongst the practitioners of the technique as to how best it should be applied. Crofton (1953) has said that " in many areas mass radiography policy at the moment is exceedingly vague, in fact it is probably flattery to call it policy at all ". It seems not unreasonable to suggest that there has been too much applied and too little basic epidemiological research.

This period of " applied " mass radiography has not, of course, been unfruitful. Very large numbers of patients were detected much earlier than they would have been otherwise; notable radiographic improvements have been made, and also two discoveries whose importance is not generally recognized. American work by Yerushalmy, Harkness, Cope & Kennedy (1950), confirmed in Great Britain by Cochrane & Garland (1952), has demonstrated the observer-errors in the diagnosis of tuberculosis revealed by variations between readings by different observers, and between readings by the same observer at different times, of small and full-size films, and has carefully evaluated techniques of reducing this error by duplicate and triplicate readings. Duplicate reading would undoubtedly increase the efficiency of mass miniature surveys, but there is little sign of its being generally adopted in Great Britain. The other discovery is really a rediscovery of the fact that when surveys are done on a voluntary basis those who have tuberculosis tend (on the average) to be less willing to come forward to be *x* rayed. The first observation of this kind seems to be that of Kayser-Petersen who in 1931 found an increasing percentage of abnormal *x* rays as increasing pressure was brought to bear on the population of Jena to come and be *x* rayed (Kayser-Petersen, personal communication, 1952). Unfortunately, this observation had only a limited circulation. Many authors have confirmed this in more recent years, for example, Bradbury (1948), Cochrane (1951), Palchanis (1952), Iskrant & Remein (1952) and Refsum (1952). There seems little doubt that it is a very general phenomenon, which probably holds for many diseases. The only disease for which the reverse has been demonstrated is coal-workers' pneumoconiosis (Cochrane, 1951).

1. Community Surveys

At the same time, there has been an attempt in various countries to use mass radiography to detect " all the cases " in a defined community. The success of such surveys is summarized in Table I.

The accuracy with which these percentage figures were measured varied in the different surveys according to the accuracy with which the *x*-rayed population was checked against the defined population. Countries vary in the extent to which census material is available. Scandinavia and Iceland appear to be the only areas where up-to-date nominal lists are always available. For the survey in Muscogee County, Georgia (Comstock, 1949), a special census was taken six months after the survey, but even this time interval introduced a serious error. In the first Rhondda Fach survey " corrected " electoral rolls were used, which were not found to be altogether free from error. For the second survey, a private census was taken about three weeks ahead of the *x* raying in each town. This was found to be eminently satisfactory.

In only one country, Iceland, was any legal power available to assist the survey teams, and it is striking that the percentage obtained by Sigurdsson (1950) at Reykjavik is one of the highest claimed and, judging from the technical details given in the various surveys, it is probably the highest actually obtained. He states that legal action was taken only once but the threat was undoubtedly effective. Large-scale surveys in Great Britain could certainly not be completed at reasonable cost without introducing some legal sanctions. Australia has recently introduced such legislation giving similar powers to the survey worker, and it will be of great interest to hear of its repercussions and results.

TABLE I. COMMUNITY SURVEYS BY MASS RADIOGRAPHY, IN VARIOUS COUNTRIES

District	Percentage of population claimed to have been *x* rayed	Reference
Township in St Louis County	82.0	Davies & Scherer (1939)
Stuttgart	98.4	Schrag (1942)
Ely, Minnesota	97.8 and 89.6	Davies, Hedberg & Fischer (1948)
Muscogee County	50.0	Comstock (1949)
Reykjavik	98.1	Sigurdsson (1950)
Gottland	99.0	Lonnerblad (1950)
Aker	78.4	Refsum (1952)
Seattle	59.5	United States Public Health Service (1952)
Washington, D.C.	49.6	United States Public Health Service (1952)
Denver	74.7	United States Public Health Service (1952)
Cleveland	59.4	United States Public Health Service (1952)
Rhondda Fach	89.4	Cochrane, Cox & Jarman (1952)
Bornholm	53.9	Olsen (1953)
Cornwall	44.0	Hargreaves (1953)

2. Factors Influencing the Success of Surveys

It is not easy to disentangle the various factors which cause people to come and be *x* rayed or to refuse. As already pointed out, the tuberculous are on the average less willing to be *x* rayed than the non-tuberculous. Another important factor determining willingness to be *x* rayed is undoubtedly age, although there appear to be differences in different areas. Of the six surveys whose results are shown in fig. 1, five suggest a fairly simple relationship between age and response. Figure 2 (lower four curves), however, shows a very different relationship for which there is as yet no adequate explanation. Figure 2 also summarizes all the evidence available about the effect of sex. It is possible that the greater success in *x* raying the males than the females in the Rhondda Fach was due to the particularly high rates for miners and ex-miners. The rates for non-miners and women were identical up to the age of 65. Comstock (1949) found a higher refusal rate amongst white people than amongst coloured and amongst those of high economic status compared with those of low. Most other survey workers have the same impression that the higher economic groups, in particular the professional classes, are more difficult to *x* ray than others, but no statistical evidence has been published. It is probable that the availability of hospital beds for the treatment of tuberculosis plays an important part in determining the response. In the Rhondda Fach survey—owing to the splendid co-operation of the Welsh Regional Hospital Board—we were very fortunate in this respect, and our impression was that this factor was of great importance.

Few of the publications give any detail—no doubt for reasons of space—about the techniques used to persuade people to be *x* rayed. In general, it would appear that the Americans, as a rule, use " high-power " general propaganda —radio, posters, processions, etc.—while Europeans rely mainly on personal contact through home visiting.

The technique used during the first Rhondda Fach survey by the Welsh Regional Hospital Board's mass miniature radiography team and a team from the Medical Research Council's Pneumoconiosis Research Unit was, first of all, to prepare the valley by means of lectures during the preceding six months. Larger meetings were held immediately before the survey and the support of all organizations in the valley obtained. The survey was also given considerable publicity in the local and national press and on the radio. Widespread poster publicity was also organized. During the survey, in each town, the names were crossed off the population lists as people were *x* rayed, and, when about 40% or 50% of the population had come forward, lists were made out of those not *x* rayed and these were visited by members of the *x*-ray teams, who explained the objects of the survey, persuaded, and where necessary arranged transport. Some came only after they had been visited six or seven times. Our impression during the survey was that the general propaganda—posters, radio, meetings—was of secondary importance and that home visiting was the most important factor in determining the success of a survey, and in the second survey just completed, we relied mainly on home visiting.

FIG. 1. PERCENTAGE OF POPULATION *x* RAYED IN SIX SURVEYS, BY AGE

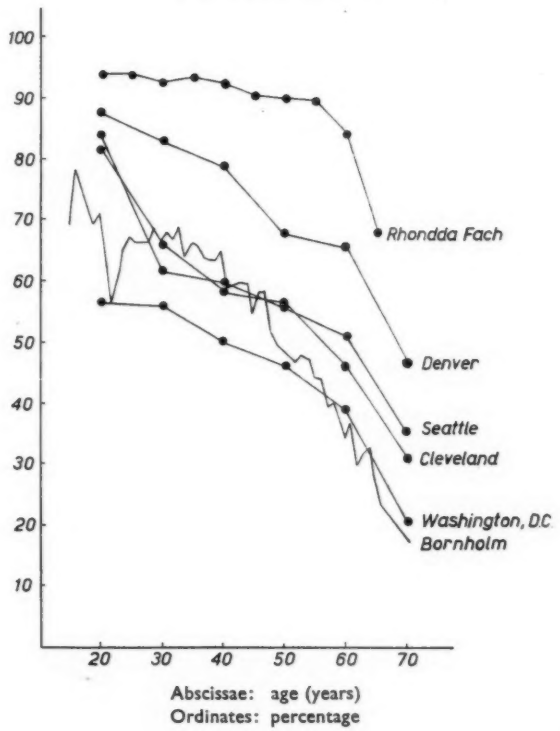
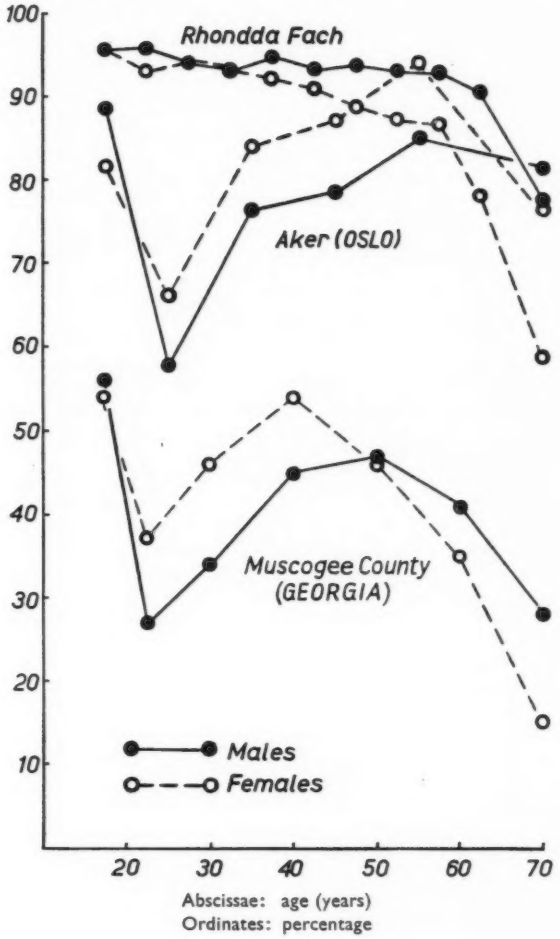


FIG. 2. COMPARISON BETWEEN PERCENTAGE OF POPULATION *x* RAYED IN THREE COMMUNITY SURVEYS



It should be stressed that the number of home visits and the long hours of work made the Rhondda Fach surveys very hard work indeed. To raise the percentage *x* rayed from about 75% to 90% very nearly doubles the amount of home visiting required. This extra effort is, however, necessary; as we have already shown, amongst the last group to be *x* rayed are many of the cases of active tuberculosis. The percentage of active cases found per 1,000 *x* rayed was higher than usual, but the cost per case, owing to the smaller average number *x* rayed per day, was considerably higher than in other surveys. It is not, therefore, a technique that can be easily put on a routine basis.

Similar techniques have, however, been used by the Welsh Regional Hospital Board's mobile team, who have succeeded in *x* raying up to 88% of some communities (Jarman, personal communication).

It is almost certain that different techniques will be effective in different countries and possibly in different areas of the same country, and it is unfortunately unlikely that rapid progress will be made in discovering the best techniques, owing to the great difficulty of doing controlled experiments. Weather and location cannot be controlled and they could only be treated as random variables in a very long series. A clerical error or a personal misunderstanding may also have a marked effect on the response in any particular area.

3. Results of Community Surveys

Ideally one would like to know the prevalence of tuberculous cases in the community surveyed, related to age and sex, and classified as "new" or "old", "infectious" or "non-infectious", and with the "non-infectious" cases classified as regards activity on some agreed reproducible international code. But this, of course, is idle dreaming. Only two of the surveys quoted mention "old" cases at all, or differentiate between "infectious" and "non-infectious" cases. Different classifications are used in Norway, Germany, the United States of America, and the United Kingdom, and even when one compares results in the same country, the marked differences suggest that the particular classification is not particularly reproducible. There is, therefore, little to be gained by comparisons, even in the rare cases where comparison is possible. Figure 3 shows a comparison between the prevalence of active and quiescent cases (old and new) in Stuttgart and in the Rhondda Fach. The difference is striking, but one is left in doubt as to whether the discrepancy is a technical artifact or an important epidemiological difference and, until there is greater international agreement about methods, progress based on such comparisons will clearly be very slow.

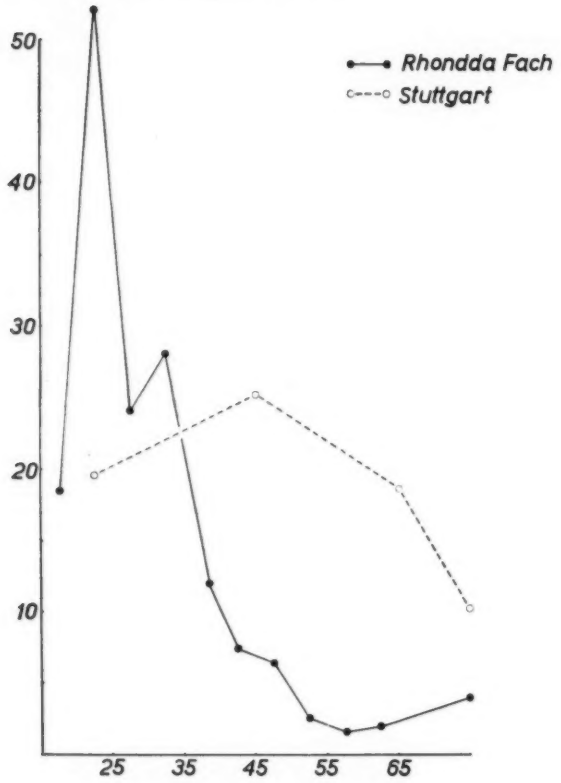
4. Effects of Such Community Surveys

Owing to the great difficulty of such surveys it is important to obtain some quantitative measure of their effect on the mortality and prevalence rate of tuberculosis and, in particular, on the rate of appearance of new cases of tuberculosis after the survey, in order to relate the latter to the percentage of the community *x* rayed and to the methods used to dispose of the infectious cases discovered at the time of the survey. It must, however, be stressed that the only way to get an accurate measure of the rate of appearance of new cases is to do another survey a few years later.

Here again the information is thin. Few surveys have been adequately "followed up" and the results of the few are not in general agreement.

The epidemiology of tuberculosis in Bornholm (Olsen, 1953) has been studied in considerable detail. Regular examinations of schoolchildren started in 1932, and in the period 1936–40 95.7% of the schoolchildren, and 71.5% of the adults up to the age of 35, were examined by *x* ray and skin tests. In addition, large numbers were given *Bacille Calmette Guérin* (BCG). Later, in 1946, an attempt was made to examine the whole population but, in spite of intensive propaganda, only 53% responded. The average notification rate for 1941–45 was 3.5 per 10,000, and for 1946–50 it was 3.4 per 10,000, so the second survey does not appear to have been particularly successful. The mortality rate has, however, been more than halved in the same period—for 1941–45 it was 2.4 per 10,000,

FIG. 3. COMPARISON BETWEEN PREVALENCE OF ACTIVE AND QUIESCENT CASES OF TUBERCULOSIS (OLD AND NEW) IN FEMALES, IN STUTTGART AND THE RHONDDA FACH



and for 1946–50 it was 1.1 per 10,000. From the scientific point of view, it is also unfortunate that the effect of BCG is inextricably entangled with the effect of discovering and isolating the infectious cases.

The first American survey (Davies, 1946) had a very optimistic result. Only two cases were found that might have been considered as " new " cases of tuberculosis developing in the community during the six years following the survey. One patient almost certainly developed the disease elsewhere and the other appeared to suffer from the spread of a lesion considered inactive at the time of the first survey. The population studied, however, was small (367). In the second survey (Davies, Hedberg & Fischer, 1948) only one new case of tuberculosis was found in a community of 6,000 *x* rayed in 1943 and 1946.

Sigurdsson (1950) has not published any detailed follow-up of the Reykjavik area, but has given a great deal of data about mortality rates, notification and infectivity data for the whole of Iceland, which can be related to the percentage *x* rayed per year. It shows that there is no very clear-cut relationship between the percentage *x* rayed in any one year and the rate of fall of the other indices in subsequent years. Refsum (1952) has published a " follow-up " of the Aker survey as regards notification, but he did not *x* ray the area again. He found that during the two years following the survey 68 new notifications (0.8 per 1,000) still occurred amongst the *x*-rayed section of the community and 151 (6.7 per 1,000) amongst the section not *x* rayed. He gives no details about mortality or notification rates before the survey. The Rhondda Fach has been resurveyed (Cochrane and colleagues, work to be published) but the results have not yet been fully analysed. We also found the second survey very much more difficult than the first. Very roughly it took four times as many hours of home visiting to achieve the same percentage in the same time.

With this meagre information it would be clearly unwise to make any but the most tentative guesses about the effect of such surveys. It seems, however, probable that the low attack rate found by Davies (1946) is exceptional, and that more dramatic effects can be expected on the mortality rate, which is affected by the early chemotherapy made possible by early diagnosis, than on the attack rate. The prevalence rate may be relatively unaffected.

There seems, on this evidence, to be a great need for more-scientifically controlled community surveys before the technique is applied on a large scale, not only to increase our epidemiological knowledge of tuberculosis but also to give us the necessary information to answer such immediate practical questions as (i) how far should a community survey be pressed, (ii) how important are the known chronic infectious cases in the community, (iii) how frequently should surveys be repeated, and (iv) is it necessary to re-examine by *x* ray all the age-groups in both sexes.

It is hoped that the Rhondda Fach survey will answer some of these questions. Although it was designed mainly to investigate the aetiology of complicated pneumoconiosis amongst coalminers, all the necessary measurements of the mortality, prevalence, and attack rate of pulmonary tuberculosis and the Mantoux conversion rate of schoolchildren will be made, and particular attention is being paid to the patients who are still infectious when they return from hospital. Two surveys of the community have already been made at an interval of two-and-a-half years, and another survey is planned later. During both the original surveys, approximately 90% of the population over the age of 15 were *x* rayed. It is not ideal. One would like to have *x* rayed 100% of the population and carried out Mantoux tests on all up to the age of 30. The Rhondda Fach is probably too atypical an area, on account of the large number of miners suffering from some degree of pneumoconiosis, so it is to be hoped that other surveys planned on similar lines will be carried out elsewhere.

5. Other Diseases

These community surveys offer excellent opportunities for the study of other pulmonary diseases. Coalminers' pneumoconiosis was studied during the Rhondda Fach survey (Cochrane, Cox & Jarman, 1952), and during the follow-up survey an attempt is being made to study bronchiectasis, carcinoma of the lung, and asthma, and it is probably in such surveys that the problem of chronic bronchitis can best be studied.

6. Summary and Conclusions

Mass miniature radiography has made possible a great improvement in the technique of detecting cases of pulmonary tuberculosis. At present, however, our knowledge of the best way to apply this technique is severely limited by our ignorance of the epidemiology of tuberculosis. It is suggested that a few community surveys, carried out with greater scientific accuracy and with adequate follow-up surveys, might answer the majority of the immediate problems.

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VACCINATION AGAINST TUBERCULOSIS WITH THE VOLE BACILLUS

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1 Historical
2 Vaccination of man with the vole bacillus
  a Safety of vole bacillus vaccine
  b Route of vaccination
  c Local reaction
  d Tuberculin sensitivity following vaccination
  e Preparation of vaccine
  f Incidence of tuberculosis in vaccinated and control unvaccinated persons
3 Discussion
References

This paper attempts to describe the reasons for using the vole bacillus as an immunizing vaccine against tuberculosis, the practical problems encountered in the experimental use of the vaccine in man and the possible advantages of the vole bacillus compared with other available antigens.

1. Historical

The vole bacillus was first found in 1937. Wells (1937) reported that a wild vole trapped alive in Scotland was found, after a short period of life in captivity in the laboratory, to be very heavily infected with an acid-fast bacillus. The macroscopic appearance of the disease was more that of tuberculosis than of animal leprosy. Later examinations of a large number of wild voles showed that the disease was widespread throughout the British Isles and in places assumed epizootic proportions, as many as 65% being infected at certain times in certain places.

The bacillus causing this disease has certain morphological differences from the classical tubercle bacilli. It was found that the bacillus could be cultured in artificial medium, but again striking differences in its cultural behaviour were seen compared with the human, bovine or avian types. Serologically, however, no distinction could be made from the human or bovine types, nor did a tuberculin prepared from the vole bacillus show any qualitative difference from human or bovine tuberculin. These facts, together with the behaviour of the bacillus in various laboratory animals, briefly to be described later, seemed to justify the classification of the vole bacillus as a new, murine type of tubercle bacillus (Wells, 1946, 1953; Brooke, 1941).

The pathogenicity of the vole bacillus for the usual laboratory animals was found to be very low. As much as 5 mg. moist weight of culture of the bacillus, when injected subcutaneously into guinea-pigs, leads only to local disease with subsequent complete resolution. It is possible, however, with massive doses subcutaneously or with less massive doses intraperitoneally to produce progressive disease which shows no pathological difference from the disease produced by the human or bovine types. Much the same experience follows injection of the vole bacillus into rabbits. They will withstand the injection of very large doses subcutaneously but smaller doses intravenously may lead to progressive disease and death. The white mouse and the rat are very resistant to infection, as also are cattle and fowls. Details of these pathogenicity experiments are given by Wells (1946), Brooke (1941), Griffith (1939, 1942), Young & Paterson (1949) and others. Voles and some other allied species, however, are extremely susceptible. As small an inoculum as 10^{-7} mg. moist weight of bacilli was found to lead to progressive infection and death, the disease resembling that found in naturally infected animals.

Although injection of the vole bacillus into laboratory animals gives rise only to local and transient disease, a high degree of tuberculin sensitivity follows, which lasts over a long period. Wells & Wylie (1952) have found, however, that tuberculin sensitivity is not co-terminous with resistance to infection. Guinea-pigs which after the injection of vole bacilli have lost their tuberculin sensitivity even for as long as six months still retain the same degree of resistance to infection with the classical mammalian tubercle bacilli. In one particular series of 11 guinea-pigs tuberculin sensitivity lasted for an average period of 330 days.

Early in the study of the vole bacillus it was found that guinea-pigs that had received an injection of bacilli showed a considerable resistance to subsequent infection with the classical mammalian tubercle bacilli (Wells & Brooke, 1940; Griffith & Dalling, 1940). This resistance does not amount to complete protection. The development of the tuberculous lesions is delayed and life is prolonged. Wells & Wylie (1952) found in one series of experiments that the average survival time of a number of guinea-pigs vaccinated with vole bacillus and subsequently infected with a virulent bovine tubercle bacillus was 163 days; a similar number vaccinated with *Bacille Calmette Guérin* (BCG) survived for 106 days, whereas the control unvaccinated animals survived for 53 days. Griffith & Dalling (1940) and Young & Paterson (1949) in a series of experiments in cattle have tested the immunizing properties of the vole bacillus as a preliminary to infection with bovine tubercle bacilli either artificially or under natural conditions in the field. They have reported very promising results.

2. Vaccination of Man with the Vole Bacillus

The story of the use of the vole bacillus in man can be divided into two parts. The first part consists of the purely experimental use of the vaccine. During this experimental period there was no standardization of methods used. The primary objects were to watch carefully the nature of the lesion following vaccination, the possible spread of the local disease throughout the body, and the development and maintenance of tuberculin sensitivity. There have, of necessity, been variations in the preparation of the vaccine and in the route and dosage of vaccination. The results of some of the preliminary work have already been published

(Wells, 1946, 1949). The second part of the story concerns the controlled clinical trials of the Medical Research Council in England and of the Tuberculosis Research Association in Africa. These trials are in progress and no results have yet been published.

a. Safety of Vole Bacillus Vaccine

No evidence of generalized disease following vaccination with the vole bacillus has been found. We have vaccinated more than 2,500 persons, and many more have been vaccinated in the clinical trials of the Medical Research Council and of the Tuberculosis Research Association. In some cases doses of vaccine far in excess of what could be conceived as the optimal dose have been given to man with no sign of disease other than local. It is, of course, possible that enormous doses might produce progressive disease in man, as they may in guinea-pigs, but we have no evidence suggestive of this. We have given 1,000 times the optimal dose intradermally to several persons with no more than a rather violent local reaction.

b. Route of Vaccination

The vaccine has been given subcutaneously, intradermally and by multiple puncture. The method to which attention has been chiefly directed is multiple puncture and the great majority of those vaccinated have received the vaccine by this route. It leads to infrequent local complications and is hardly susceptible to human error in administration. The criticism that vaccination by multiple puncture is unscientific, because the number of bacilli entering the tissues is unknown, becomes largely invalid as the method gives consistent results. It may well be that intradermal vaccination with the vole bacillus will prove to be superior to vaccination by multiple puncture in giving an even more sustained period of tuberculin sensitivity. We have not yet got evidence of this, nor are our numbers of intradermal vaccinations large enough for statistical analysis.

c. Local Reaction

The local reaction in 50 persons given the vaccine subcutaneously was severe. Ulceration, sometimes extensive, occurred in all. This route was early abandoned.

The local reaction in 194 persons given the vaccine intradermally consisted, in 188 persons, of a small papule in which skin breakdown frequently occurred for a short period. This reaction was in no way different from that seen in persons given BCG intradermally. In six persons there was an abnormal reaction, manifested by glandular enlargement and abscess formation. There seems to be a direct relationship between the abnormal local reactions and the dosage of vaccine. We find that 0.0001 mg. injected intradermally gives satisfactory tuberculin sensitivity and a minimal local reaction. No case of glandular enlargement or abscess formation has occurred with this dosage. Larger doses increase the incidence of local complications.

The local reaction following multiple puncture consisted in 2,067 persons of a series of small raised papules, which persist for some months. These eventually become pin-point white scars or disappear altogether. Of these 2,067 persons, 93% showed this normal local reaction. There is frequently a small enlargement of the local lymph glands but this is so slight and transient that it is necessary to examine the vaccinated person with his clothes off and lying down. This lymph-gland enlargement is undoubtedly of more frequent occurrence than is recorded in the literature of BCG vaccination because it has to be most carefully looked for and is of no practical importance.

The abnormal local reactions following vaccination with the vole bacillus by multiple puncture are considerable enlargement of the local lymph glands, which may take several weeks to resolve to their normal size; the development of an abscess in the local lymph glands, which may resolve spontaneously but more frequently either evacuates itself or has to be evacuated surgically; the development of a lupoid reaction at the site of vaccination. The incidence of glandular abscess in those persons vaccinated by multiple puncture has been 0.2%. All these have resolved with appropriate local treatment. It is interesting to record that five out of six of these glandular abscesses have been in girls who have been vaccinated in the thigh. It seems probable that secondary infection plays an important part in the breakdown of the local lymph glands in these cases. The lupoid reaction consists of a raised purplish area at the site of inoculation. The skin looks and is unhealthy and may from time to time break down into small shallow ulcerated areas. Biopsy shows a typically tuberculous reaction in the affected tissue. This lupoid condition is undoubtedly closely linked with secondary infection. All the cases we have seen have been in mental defectives whose physical habits are dirty, with a varying degree of incontinence of urine and faeces. We have never seen the condition in any of the normal persons who have been vaccinated. Of all those vaccinated, 3.3% have developed a lupoid reaction varying from an area less than 2 mm. to 3 cm. in diameter; 88% of the total number of lupoid reactions occurred in one institution where the vaccinated were young, low-grade defectives and the nursing staff was greatly depleted. The condition has been troublesome to treat but has resolved in time.

d. Tuberculin Sensitivity following Vaccination

With the exception of two persons, all those vaccinated with the vole bacillus, by whatever route and in the varying doses used, showed sensitivity to 100 international tuberculin units (TU) of Old Tuberculin. The percentage showing tuberculin conversion is 99.9. The two cases that did not develop sensitivity were both shown by the technique described by Wells & Wylie (1949) to have a tuberculin-neutralizing factor in their blood serum. The degree of tuberculin sensitivity and the speed of conversion have varied with the dosage and the condition of the culture used for preparing a vaccine. Reference to this latter fact will be made later when the preparation of the vaccine is considered. The great majority of those vaccinated by multiple puncture through a suspension containing 2 mg. or more moist weight of bacilli per millilitre showed a positive reaction to 1 TU.

A comparative trial of BCG and vole bacillus in nurses, medical students and schoolchildren has been reported by Hall & Wylie (1952). They used the technique of multiple puncture. The suspension of BCG was 20 mg. per millilitre and that of vole bacillus 2 mg. per millilitre. They report satisfactory tuberculin conversion, using 100 TU seven weeks after vaccination. Using 10 TU, they obtained, after the same period of time, a conversion of 45% with BCG and 70% with vole bacillus. They state that vaccination by multiple puncture gives less initial discomfort and fewer undesirable sequelae than occur with intradermal injection.

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TABLE I. VACCINATIONS WITH VOLE BACILLUS: REVERSION RATES

Period when tested (after vaccination)	Total number of persons tuberculin tested	Tuberculin-positive		Tuberculin-negative	
		Number	Percentage	Number	Percentage
During 1st year	243	242	99.6	1	0.4
During 2nd year	1,981	1,926	97.2	55	2.8
During 3rd year	1,511	1,432	94.8	79	5.2
During 4th year	986	875	88.7	111	11.3
During 5th year	182	152	83.5	30	16.5
During 6th year	110	99	90.0	11	10.0
During 7th year	63	53	84.1	10	15.9
During 8th year	48	34	70.8	14	29.2

Reversion from the induced tuberculin sensitivity has again varied with dosage and the vaccine used. The over-all figures are given in Table I.

These figures may usefully be subdivided into groups.

A group of persons in the same institution were vaccinated intradermally, 118 with 0.0001–0.0002 mg. of vole bacilli and 112 with 0.075 mg. of BCG prepared by the State Serum Institute at Copenhagen. The two groups were comparable as regards age and sex and were all vaccinated the same day. The condition of tuberculin sensitivity 12–14 months after vaccination is shown in Table II.

Table III shows the reversion rates for 1,734 persons vaccinated by multiple puncture through a suspension containing 2–5 mg. moist weight of bacilli.

It seems that a vaccine containing 2 mg. moist weight of bacilli is near the optimum if the objective is satisfactory tuberculin conversion and minimal incidence of complications following vaccination.

Table IV shows the reversion rates for 417 persons vaccinated by multiple puncture through a suspension containing 0.1–1 mg. moist weight of bacilli.

The reversion rates with this dosage of vaccine are higher than with the larger dosage.

e. Preparation of Vaccine

The vole bacillus has certain growth characteristics which distinguish it from either the human or bovine type. In primary culture, and to a great extent in subculture, growth is inhibited by glycerine. This means that many of the media, and particularly the fluid media, used for the culture of tubercle bacilli are of no use for the cultivation of vole bacilli. Growth takes place, slowly but with reasonable abundance, on Dorset egg medium without glycerine. Preparation of vaccine has been confined to the growth from this medium. The bacillary mass is scraped off with a platinum spatula and ground up either in a Griffith's tube or a homogenizer similar to that described by Pierce, Dubos & Schaefer (1953). The diluent now used for the vaccine is 0.1% human serum albumin in distilled water. A small quantity of Tween 80 in the diluent has been tried but no obvious advantage accrued either in the initial dispersion of the bacilli or in the maintenance of a dispersed suspension. The preservative quality of serum albumin on the viability of tubercle bacilli in suspension has been reported by Fenner (1951) and his results have been confirmed with the vole bacillus.

The maintenance of virulence of the vaccine strain is of the greatest importance. As the vole bacillus is a natural pathogen of voles, the maintenance of virulence is an easier matter than it is with fully virulent human or bovine strains whose virulence has been reduced by cultural means until they are no longer pathogenic to laboratory animals. A stock of laboratory-bred voles has been available throughout the period of the experimental work with the vole bacillus. It has been found necessary to infect voles and re-isolate the vaccine strain at frequent intervals in order to maintain the full degree of virulence of the vole bacillus for voles. A culture that has had more than 10 passages in artificial medium since isolation from a vole is not now used for vaccine preparation. The effect of using as a vaccine a culture that has had more than 10 passages in artificial medium on the tuberculin reversion rate in vaccinated persons is shown in Table V.

TABLE II. INTRADERMAL VACCINATIONS: TUBERCULIN SENSITIVITY 12–14 MONTHS AFTER VACCINATION

Tuberculin sensitivity	Vole bacillus		BCG	
	Number of persons tested	Percentage tuberculin-sensitive	Number of persons tested	Percentage tuberculin-sensitive
Positive to 1 TU .	97	82.2	69	61.6
Negative to 1 TU; positive to 100 TU . . .	19	16.1	38	33.9
Negative to 100 TU	2	1.7	5	4.5

TABLE III. VACCINATIONS WITH VOLE BACILLUS: REVERSION RATES FOR 1,734 PERSONS
(Multiple puncture vaccinations through suspension of 2 mg. or more)

Period when tested (after vaccination)	Total number of persons tuberculin tested	Tuberculin-positive		Tuberculin-negative to 100 TU	
		Number	Percentage	Number	Percentage
During 1st year	184	183	99.5	1	0.5
During 2nd year	1,326	1,313	99.0	13	1.0
During 3rd year	1,063	1,019	95.9	44	4.1
During 4th year	803	726	90.4	77	9.6
During 5th year	172	142	82.6	30	17.4
During 6th year	67	61	91.0	6	9.0
During 7th year	35	29	82.9	6	17.1
During 8th year	32	24	75.0	8	25.0

f. Incidence of Tuberculosis in Vaccinated and Control Unvaccinated Persons

The experimental vaccinations in man reported here cannot give any conclusive answer to the degree of resistance to clinical tuberculosis following vaccination. The clinical trials at present in progress in England and in Africa were

TABLE IV. VACCINATIONS WITH VOLE BACILLUS: REVERSION RATES FOR 417 PERSONS
(Multiple puncture vaccinations through suspension of less than 2 mg.)

Period when tested (after vaccination)	Total number of persons tuberculin tested	Tuberculin-positive		Tuberculin-negative to 100 TU	
		Number	Percentage	Number	Percentage
During 1st year	17	17	100	0	0
During 2nd year	387	371	95.9	16	4.1
During 3rd year	367	342	93.2	25	6.8
During 4th year	175	142	81.1	33	18.9
During 5th year	2	2	—	0	—
During 6th year	34	29	85.3	5	14.7
During 7th year	19	15	78.9	4	21.1
During 8th year	16	10	62.5	6	37.5

designed to supply this information. Nevertheless it may be of interest to give the results so far. There have been three cases of tuberculosis in the 2,500 vaccinated persons. One of these died and should not be included in the series, because it is quite clear that infection with the human tubercle bacillus occurred before vaccination. Owing to an oversight nearly three months elapsed between tuberculin testing and vaccination. An accelerated reaction followed vaccination, reaching its maximum at 10 days. Twenty-eight days after vaccination the patient showed a strongly positive reaction to 1 TU. He died six months after vaccination. Human tubercle bacilli were recovered at post-mortem examination. One person developed pulmonary tuberculosis from which he recovered and the third developed a transient tuberculous endometritis. From both these, human type tubercle bacilli were isolated. This gives an incidence in the vaccinated of 0.085%.

In the control group, which consisted of an equal number of persons of the same age and sex in those institutions in which a controlled study could be made and who were negative to 100 TU at the start of the experimental period, there have been 17 cases of tuberculosis, of which 4 have died, out of a total of 717. Human type tubercle bacilli have in each case been isolated. This gives an incidence of 2.35%. In the vaccinated the incidence of tuberculosis has therefore been only about one twenty-eighth of that in the control group. The incidence of tuberculosis in the control group may appear to be unduly high but it must be remembered that the very great majority are mental defectives in whom the incidence is known to be high, and the figures cover a period of years.

3. Discussion

In considering the possible use of the vole bacillus as a vaccine against tuberculosis, it is not only necessary to establish theoretical and practical advantages over BCG—about which much is known and experience with which is so wide—but also to consider the aims of vaccination in man. The vole bacillus is a natural pathogen causing disease which is certainly widespread in Great Britain and possibly elsewhere. This disease, although widespread, appears to be confined to a small number of species of animals. Further, the pathogenicity of the bacillus, except for its host, is low for laboratory animals and for man, but is nevertheless considerably higher than that of BCG. It seems likely that the virulence of the vole bacillus is reasonably steady and that its emergence as a distinct type of tubercle bacillus with morphological and cultural differences from the other types is settled. If this is accepted, then we are dealing with a bacillus whose virulence cannot be exalted by artificial means but can be kept comparatively steady by passage through its natural host. No question of attenuation before use as a vaccine arises. It is very different with BCG. Here a virulent bovine tubercle bacillus has become artificially attenuated to a stage of " virulence " where it is no longer capable of causing progressive disease in animals or man. The maintenance of a level of " virulence " by animal passage is therefore impossible. The danger of an exaltation of virulence in BCG seems extremely remote but the converse of a fall in virulence to a point where antigenicity is lowered appears theoretically much more possible. We suggest, therefore, that the vole bacillus has a theoretical advantage over BCG.

In practice we have found that the vole bacillus injected into animals or man by the same route, whether it be subcutaneously, intradermally or by multiple puncture, gives rise to a higher and more lasting tuberculin sensitivity than does BCG. It would appear from animal experiments that this higher level of sensitivity is accompanied by a higher level of resistance to tuberculous infection. Moreover, the induced resistance outlasts sensitivity in guinea-pigs (Wells &

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TABLE V. VACCINATIONS WITH VOLE BACILLUS: REVERSION RATES
(Multiple puncture vaccination)

Period when tested (after vaccination)	Using vaccine of less than 10th generation					Using vaccine of 10th or subsequent generation				
	Total number of persons tuberculin tested	Tuberculin-positive		Tuberculin-negative to 100 TU		Total number of persons tuberculin tested	Tuberculin-positive		Tuberculin-negative to 100 TU	
		Number	Percentage	Number	Percentage		Number	Percentage	Number	Percentage
During 1st year	195	194	99.5	1	0.5	8	8	—	0	—
During 2nd year	1,475	1,462	99.1	13	0.9	332	298	89.7	34	10.3
During 3rd year	1,223	1,175	96.1	48	3.9	245	216	88.1	29	11.9
During 4th year	796	723	90.8	73	9.2	182	145	79.7	37	20.3
During 5th year	128	110	85.9	18	14.1	46	34	73.9	12	26.1
During 6th year	91	80	87.9	11	12.1	10	10	—	0	—
During 7th year	48	39	81.3	9	18.7	6	5	—	1	—
During 8th year	42	30	71.4	12	28.6	6	4	—	2	—

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RELATIONSHIP BETWEEN HOST CELL AND PARASITE IN TUBERCULOSIS

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1 Growth in cells of tubercle bacilli of varying virulence
2 Growth of tubercle bacilli in cells from immunized animals
3 Role of the mononuclear phagocytes in native resistance
References

In order to produce a tuberculous lesion in the body, tubercle bacilli must grow within phagocytic host cells. The success of the initial parasitization of cells determines in most instances the outcome of the infective process. It is therefore necessary that the relationships between tubercle bacilli and the cells in which they grow should be thoroughly examined.

Although experimental systems in which the host cells have been isolated from the body have long been recognized as a useful method of approach to this problem, progress has been hampered by lack of methods for growing the tubercle bacillus in a form suitable for experiments of this sort. The addition to liquid media of non-ionic detergents has made it possible to grow tubercle bacilli in a dispersed state. Suspensions prepared from such cultures contain relatively large numbers of single bacilli, almost all of which are viable. This greatly facilitates the quantitative parasitization of living host cells. In the past it has been necessary to prepare bacterial suspensions from cultures that have often been grown for long periods, and that have been subjected to damaging operations in order to disperse the organisms. Bacilli obtained in this way were of unknown viability, and were not in a uniform physiological condition.

Despite these limitations, the earlier studies on cell-parasite relationships in vitro have added significantly to our understanding of tuberculosis.

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1. Growth in Cells of Tubercle Bacilli of Varying Virulence

Differences in the pathogenicity of virulent strains of tubercle bacilli can be measured by differences in survival time of a susceptible host species. But differences in the pathogenicity of attenuated strains could, until recently, be measured only by crude estimates of the amount and nature of the cellular reaction they produced in the tissues, or by the degree of tuberculin sensitivity they produced before being destroyed.

A much more sensitive measure of virulence has recently been demonstrated in the studies of Pierce, Dubos & Schaefer (1953), who graded the pathogenicity of both virulent and attenuated strains by their capacity to produce lesions in the tissues of the mouse. With this criterion they were able to show that tubercle bacilli introduced into the tissues of mice grow at rates which are characteristic of their virulence. In the spleen for instance, the more virulent the bacilli are, the more rapid is their initial rate of multiplication, and the greater is the maximum population density reached by the bacilli. Eventually the defence mechanisms of the host prevent the further multiplication of even virulent bacilli in this organ.

Mackaness, Smith & Wells (1954) have shown that in isolated monocytes in vitro a similar relation holds between the growth-rates of tubercle bacilli of varying degrees of virulence. These studies, which were carried out in rabbit monocytes, showed that the more virulent the bacilli are, the shorter is the latent period before they begin to multiply; moreover, virulent bacilli appeared to have a shorter generation time within cells. Attenuated bacilli, in addition to having

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VOLE BACILLUS VACCINATION AGAINST TUBERCULOSIS

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Wylie, 1952), whereas the resistance following BCG vaccination is waning when sensitivity is lost and has disappeared six months later. Whether this applies to man is, of course, a matter of conjecture.

The aim of vaccination against tuberculosis in man appears to be the development of the highest level of resistance to the disease combined with safety and a minimum of local or general disturbance. It seems probable that the highest level of resistance would follow infection with a fully virulent mammalian tubercle bacillus. This, however, is clearly impracticable, because a certain proportion of persons so infected would develop progressive and generalized disease as well as extensive local disturbance. The margin of safety with BCG is undisputed but may it not be too great to allow the development of maximum resistance? The greater virulence of the vole bacillus seems to us to present an advantage. The margin of safety may well be less than with BCG but we have no evidence whatever that it is inadequate.

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a long lag period, often 10 to 14 days, were found to be more susceptible to intracellular digestion. When the growth-rates of the same strains of tubercle bacilli were measured in the livers and spleens of living mice, a relation was found between growth-rates in vivo and those found in isolated monocytes in vitro (Table I). It would appear therefore that an isolated monocyte culture is a model of conditions in vivo before they become complicated by the development of acquired resistance. In the light of this, it seems possible to interpret virulence as the capacity of tubercle bacilli to survive and multiply in an intracellular environment.

TABLE I. COEFFICIENTS OF INCREASE IN THE NUMBERS OF TUBERCLE BACILLI OF FOUR STRAINS IN MOUSE ORGANS IN VIVO AFTER INCUBATION FOR EIGHT DAYS, AND IN ISOLATED RABBIT MONOCYTES IN VITRO AFTER INCUBATION FOR FIVE AND SEVEN DAYS*

Strain of tubercle bacilli	Mouse organs (after 8 days)		Rabbit monocytes	
	Spleen	Liver	After 5 days	After 7 days
H37Rv . .	152	33	5.7	>20
RIRv . .	21	2.3	1.9	2.7
H37Ra . .	17	1.8	1.0	1.8
BCG . .	3.4	1.7	0.6	—

* From Mackaness, Smith & Wells (1954).

Monocytes do not provide optimal nutritional conditions for tubercle bacilli. This is illustrated by infecting monocytes with bacilli prepared from Tween-albumin cultures that have been grown for three or more weeks. In a complete medium such bacilli grow almost as readily as bacilli obtained from young cultures in their logarithmic growth phase (Fenner & Leach, 1953). But in isolated monocytes bacilli obtained from Tween-albumin cultures of increasing age show a proportional increase in the latent period before they begin to multiply. Virulent bacilli from aged cultures show only a slight increase in their lag period; but the most attenuated strains, although known to be alive at the time of ingestion, may not grow at all. Thus aged bacilli of the strain *Bacille Calmette Guérin* (BCG) fail to multiply and may be largely destroyed by the monocytes in a period of two or three weeks (Mackaness *et al.* 1954).

This effect of the physiological state of tubercle bacilli upon growth within isolated monocytes is also paralleled by the behaviour of aged bacilli growing in the tissues of living animals. Bloch (1950) and Fenner & Leach (1953) have shown that the pathogenicity of tubercle bacilli, as measured by the survival time of the host when it is infected with virulent bacilli, or by the number and size of the lesions when the host is infected with attenuated strains, declines with increasing age of the culture used for inoculation.

Earlier qualitative studies on the growth of tubercle bacilli in tissue culture or in surviving cell preparations did not dissociate intracellular and extracellular multiplication. With few exceptions, however, the results of these studies are consistent with the view that virulent bacilli grow within cells more readily than do attenuated bacilli. Eighteen studies of this type have been found. In eleven experiments in which the strain of organism was stated to be of low virulence, the bacilli grew slowly or not at all in nine. In eight of nine studies in which mammalian strains of high virulence were used the bacilli were said to grow rapidly and destroy the living host-cell population. In two studies virulent avian bacilli were found to grow slowly in tissue culture preparations. In one of these Fell & Brieger (1947) found, with chick embryonic tissue, a slow multiplication of avian bacilli of all degrees of virulence. The uniformly slow growth-rate of virulent and attenuated bacilli may have resulted in these experiments from the low temperature of incubation. The normal temperature of the natural host of avian bacilli is high (42° C.). It is possible that growth-rates were limited by the suboptimal temperature rather than by the availability of some specific growth requirement of the bacilli.

Suter (1952) has recently published observations which showed that, although multiplication of bacilli of an avirulent strain did not occur in isolated monocytes, attenuated bacilli grew as rapidly as virulent bacilli. It is probable that the technique used in this study did not compare the true relative growth-rates of intracellular bacilli (Mackaness *et al.* 1954).

At present there is little indication of what the conditions are that determine the characteristic behaviour of intracellular tubercle bacilli, but it seems possible to analyse them further. Progress has already been made in this direction. Dubos (1953) has shown that, under conditions of low oxygen tension, or in the presence of high concentrations of hydrogen ions, tubercle bacilli are sensitive to certain organic acid metabolites, particularly lactic acid. In these experiments attenuated bacilli seemed to be more susceptible than virulent bacilli to the toxic effect of these substances. The accumulation of products of anaerobic glycolysis is likely to occur in areas that are densely populated by living mononuclear phagocytes. If this were demonstrated experimentally it would go far towards explaining the marked differences in the growth-rate in vivo of tubercle bacilli of varying degrees of virulence.

2. Growth of Tubercle Bacilli in Cells from Immunized Animals

The monocyte is usually thought of as the instrument of defence against the tubercle bacillus. Two types of change have been said to occur in the mononuclear phagocytes of immunized animals. One appears non-specific and expresses itself in a greater capacity for phagocytosis, and an increased rate of cell division and mobilization at sites of irritation (Lurie, 1939). Phenomena such as these can be found associated with the lesion of reinfection. They would seem to result from the hypersensitive state of the tissues in general, and not, as has been suggested, from an altered physiological state of the phagocytes themselves.

The second change which has been postulated to occur in the phagocytic cells of immunized animals is a specific antituberculous function directed against ingested bacilli. The evidence in support of a cellular immunity of the second type derives largely from morphological studies. When conditions are favourable to the host it is from the cytoplasm of the mononuclear host cells that tubercle bacilli are seen to disappear. Metschnikoff (1888) was perhaps the first to emphasize this fact, and from it there has arisen the rationalization that the mononuclear phagocytes of immunized animals have

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an acquired capacity to limit the multiplication and to destroy bacilli which have been ingested by them. The objective evidence upon which this view is based appears inadequate.

In quantitative experiments with surviving monocytes the relative growth-rates of both virulent and attenuated tubercle bacilli have been compared in monocytes from normal and from immunized rabbits (Mackaness, 1954). No evidence could be found in these studies for an antituberculous immunity in the monocytes of immunized animals. Results are given from two representative experiments (see Table II).

TABLE II. NUMBERS OF TUBERCLE BACILLI OF TWO STRAINS, VIRULENT BOVINE TYPE BRANCH AND ATTENUATED HUMAN TYPE R1Rv, IN MONOCYTES FROM NORMAL AND H37Rv-IMMUNIZED RABBITS BEFORE AND AFTER THE ONSET OF BACTERIAL MULTIPLICATION IN MONOCYTE CULTURES IN VITRO *

Period of incubation of monocyte culture (days)	Source of monocytes	Average number of bacilli per infected monocyte	Average number of bacilli per monocyte of total population	Percentage of monocytes infected	Percentage of monocytes containing more than 20 bacilli	Coefficients of increase
Strain : Branch						
1	Normal rabbit	4.5	2.2	49	0.4	—
	Immunized rabbit	5.3	2.7	51	0	—
3	Normal rabbit	7.9	5.3	67	9.8	2.4
	Immunized rabbit	8.6	5.8	68	4.9	2.2
Strain : R1Rv						
1	Normal rabbit	6.3	4.3	68	0.5	—
	Immunized rabbit	4.6	3.0	65	0.7	—
5	Normal rabbit	7.5	6.4	75	6.7	1.5
	Immunized rabbit	6.3	4.8	72	5.1	1.6
8	Normal rabbit	13.6	12.6	93	30	2.9
	Immunized rabbit	11.6	10.7	93	26	3.6

* Modified from Mackaness (1954).

They show that the rate of increase in bacterial numbers was as high in " immune " as in normal rabbit monocytes. In other experiments of the same type it was found that the lag period of aged bacilli was the same in monocytes from immunized animals as in those from normal animals. This was determined by comparing the time taken for regressed bacilli to change from a cocco-bacillary to an elongated form within monocytes from normal and from immunized rabbits. In the case of a virulent bovine type bacillus this pre-multiplication phase lasted approximately 24 hours in both sets of monocyte cultures. The change in morphology undergone by regenerating bacilli in monocytes from an immunized animal is shown on Plate I, figs. A and B. It would appear, therefore, that the autosynthetic activities of tubercle bacilli are in no way hindered in monocytes which have been isolated from the bodies of immunized animals.

There have been very few reported studies on the growth of bacilli in cells from immunized animals. Suter (1953) has published results from experiments on the growth of tubercle bacilli in monocytes from normal and from immunized guinea-pigs and rabbits. He found marked, or even total, inhibition of multiplication in monocytes from immunized animals. No control was kept of the number of monocytes present in the cultures during these experiments, so that Suter's results are difficult to interpret.

Kallós (1941) mixed tubercle bacilli with exudative mononuclear cells in normal and immune plasma and allowed the mixture to clot in Carrel flasks. In the presence of " immune " monocytes in normal plasma, Kallós observed that the " multiplication of bacilli may possibly have been a little retarded ". But when " immune " cells were mixed with immune plasma no bacterial multiplication was observed. This important observation requires confirmation, for there have been several reports that certain organisms are susceptible to intracellular digestion only after sensitization with immune serum (Spink & Keefer, 1937; Zinsser, Enders & Fothergill, 1939). In short-term experiments Hanks & Evans (1940) introduced tubercle bacilli into blood cell-serum mixtures from immunized animals, but could demonstrate no effect upon the viability of the bacilli after a period of exposure.

Brieger, Fell & Smith (1951) infected rabbits with virulent bovine type bacilli by intravenous or intrasplenic inoculation. Bacilli grew more rapidly in splenic explants removed from the body 6–17 days following infection than in those removed in the first 6 days. The more rapid growth of bacilli in the later explants did not appear to result from the presence in them of larger numbers of bacilli; these were few in number in the mononuclear cells migrating from tissue explanted at all stages of the infection. These observations indicate that no antituberculous immunity was present in the mononuclear phagocytes of tuberculous animals. Indeed the explosive nature of the bacterial growth which occurred in explanted tissue suggests a release from some restraining influence which was present in the organ in situ, but was lost when the tissues were explanted in vitro.

Evidence from in vitro studies seems, therefore, to oppose the view that a specific antituberculous immunity exists in the mononuclear phagocytes of immunized animals; and certain experiments in vivo also cast doubt upon its existence. Although Lurie (1929) has claimed that bacilli at the site of reinfection are quickly destroyed without preliminary multiplication, this has been denied by Freund & Angevine (1938). Reliable quantitative methods are now available for the enumeration of viable tubercle bacilli in the tissues (Fenner, Martin & Pierce, 1949), and it is possible to provide an answer to this important question. Recent studies by Dubos, Pierce & Schaefer (1953) showed no evidence of a rapid destruction of bacilli in the tissues of immunized mice, but they did reveal

the existence of an immunity which acts by restraining the growth of bacilli. These studies were not concerned with the early phases of bacterial multiplication in the tissues of the immunized animal, and no information was obtained of what happens to bacilli immediately after they have been introduced into immune tissues.

Schaefer, Pierce & Dubos (personal communication, 1953) injected mice with small numbers of two virulent strains of tubercle bacilli, one eugonic and the other dysgonic. The two strains could be distinguished by their colonial form. Following injection of bacilli of the eugonic strain, the bacterial count in the spleen rose to a maximum beyond which no further multiplication occurred. At this time bacilli of the dysgonic strain were injected, and there followed a small but definite multiplication of bacilli of the second inoculum. This observation shows that resistance to the growth of tubercle bacilli does not develop uniformly throughout the tuberculous spleen. Apparently a new defence must be built up against each new invasion of the tissues. This defence is perhaps a local one, dependent upon changes which occur at the site of implantation of bacilli, and evolved during the development of the lesion. In the immunized or tuberculous animal these changes appear to occur more rapidly.

Without the postulation of the existence of an intrinsic immunity in the mononuclear cells of the immunized host, it still remains possible, therefore, that a local immunity develops within the lesion, and that it is dependent upon the normal functional activities of the monocyte-epithelioid cells of the tubercle. Some observations in vitro might tend to support this view (Mackaness, unpublished observations, 1953). The rate of multiplication of tubercle bacilli in monocyte cultures in vitro has been found to depend upon, among other things, the density of the monocyte population. The observed growth-rate of intracellular bacilli was found to fall as the density of the monocytes was increased. It is significant that the greater the degree of attenuation of the bacilli the greater was the degree of inhibition observed under conditions of monocyte crowding. Experiments to show this phenomenon are technically difficult to perform, and some doubt still exists concerning the general validity of the findings. None the less, it seems likely that a similar effect may occur in vivo, and that the density of the monocyte-epithelioid cell population of a consolidated tubercle may be a factor controlling the rate of increase in bacterial numbers. Reference has already been made to the possible effect upon bacterial growth of the accumulation of metabolic products in areas of monocyte crowding. This suggests a mechanism whereby the normal activities of the host cell could be directed against the parasite and the reason why attenuated bacilli grow less abundantly in vivo than do virulent bacilli.

There are obviously many other factors which must be considered as possible causes for the restriction of bacterial multiplication that occurs in the tissues of immunized animals. Among them is the part played by humoral factors, for these have not yet been excluded from a role in immunity against the tubercle bacillus.

3. Role of the Mononuclear Phagocytes in Native Resistance

Host species vary greatly in their resistance to infection by mammalian strains of tubercle bacilli. The rat is almost totally resistant to infection by virulent bacilli of both mammalian types. The rabbit, susceptible to virulent strains of bovine type, is highly resistant to infection by human type bacilli; while the guinea-pig is highly susceptible to infection by both types.

So far as this author is aware there is no evidence to dissociate native and acquired immunity, at least in respect to tubercle bacilli of mammalian origin. In the rat, despite its enormous resistance, tubercle bacilli are known to multiply extensively in the tissues during the early stages of infection (Wessels, 1941). It is only when lesions develop that multiplication ceases, and destruction of bacilli ensues. The same appears true of the rabbit infected with human type bacilli (Lurie, 1928).

If immunity, native or acquired, is dependent upon the capacity of the host's phagocytic cells to restrain the growth of intracellular tubercle bacilli, then the growth characteristics of tubercle bacilli within isolated monocytes from host species of varying native resistance might be expected to differ. So far satisfactory experimental techniques for the demonstration of such differences have not been found. It is apparent, however, that any difference which it may be possible to demonstrate between monocytes of different animal species will not be large. This is seen from the fact that even attenuated bacilli of human type (R1Rv) can multiply within rabbit monocytes, provided the density of the monocyte population is not too high.

Obviously the isolated monocyte preparation is not an adequate model of conditions in vivo, nevertheless it has been shown that virulent bacilli of one strain of bovine type (Branch) grow with a shorter latency in rabbit monocytes than do virulent bacilli of one strain of human type (H37Rv). But the difference found between these strains was small. It follows that the unfavourable conditions encountered by bacilli within phagocytic host cells must be greatly exaggerated in the animal body if they are to explain the whole of the difference in pathogenicity for the rabbit of these two human and bovine type bacilli. This emphasizes our ignorance of the conditions which prevail within a tuberculous lesion, and of the factors responsible for the varying susceptibility of different host species, and the small but definite degree of acquired resistance that develops even in the most susceptible animal species following vaccination.

The problems involved in immunity to the tubercle bacillus are made more complex by the occurrence of tissue necrosis. But it should be emphasized that before necrosis occurs it is the mononuclear phagocyte that is the immediate environment of the tubercle bacillus; and in man it must often happen that the relations between host and parasite never proceed beyond this simplified problem. It is for this reason that the present discussion has taken a restricted view of host-parasite relationships in tuberculosis.

In summary it may be said that the capacity of tubercle bacilli to survive and multiply within the phagocytic cells of a host appears to be related to their virulence. This capacity seems to vary inversely with the age of the infecting bacilli and the degree of monocyte crowding. The more attenuated the bacilli are, the more marked do these effects become. In the immune state no generalized change appears to occur in the phagocytic cells of the animal tissues. But changes, possibly related to the degree of monocyte crowding, may take place within the host cells of a developed lesion. We are largely ignorant of the nature of these changes but with improved techniques they can be studied experimentally.

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SOME EXPERIMENTAL APPROACHES TO THE TUBERCULOSIS PROBLEM

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1 Effect of cortisone on tuberculosis
2 Antituberculosis action of certain surface-active polyoxyethylene ethers
References

Although under some conditions progressing rapidly, tuberculosis is generally characterized by a prolonged course with a marked tendency towards periods of exacerbation and relapse. Hitherto the main experimental approaches and the main advances have resulted from a study of the tubercle bacillus. On the other hand, the very nature of the infection, with its complicated host-parasite interrelationship, would suggest that a study of factors influencing the susceptibility of the host, whether favourably or unfavourably, might be rewarding. Since we know little or nothing of the factors concerned in these natural variations, it is reasonable to seek for alterations by artificial chemical means, but until recently this has led to little success. Encouragement has, however, been given to continued search in this direction by the clinical observation of the efficiency of calciferol in lupus vulgaris, where certainly the drug has no direct action against the tubercle bacillus, but may enhance the specific cellular reaction to it. More recent experimental studies have shown that certain steroids produce an unfavourable effect on the outcome of a tuberculous infection by virtue of their action on the host, while some surface-active agents produce a powerful therapeutic effect and the weight of evidence suggests they too act in some way on the host. These two discoveries are discussed in the present article.

1. Effect of Cortisone on Tuberculosis

An enhancing effect of cortisone upon the course of a tuberculous infection in animals was demonstrated by Hart & Rees (1950) of the National Institute for Medical Research, London. The effect was produced upon both acute and chronic types of tuberculosis in the mouse infected with a virulent human strain of organisms. In acute tuberculosis, cortisone treatment produced early deaths from a fulminating infection at a time when the untreated control mice were still alive. The chronic type of infection was one especially developed to assess factors that might increase susceptibility to tuberculosis, and was produced with approximately one-hundredth of the dose of tubercle bacilli used to produce the acute disease. After six weeks the resulting disease was predominantly a pulmonary infection, characterized by small discrete proliferative lesions containing scanty tubercle bacilli, which remained relatively non-progressive for a period of at least eight weeks (Plate I, fig. C). A three-week course of cortisone, administered during this period, caused the breakdown of these lesions, with the formation of large coalescing necrotic lesions teeming with tubercle bacilli and resulting in a high mortality (Plate I, fig. D). Whereas in the acute infection cortisone had presumably increased the susceptibility of the host to what was a rapidly progressive and fatal infection, in the chronic, more or less stable infection, cortisone had completely disorganized the natural host-parasite relationship, with the outcome overwhelmingly in favour of the tubercle bacillus. This stable chronic type of infection has been used to test the possible enhancing effect of other hormones, synthetic compounds or diets. In particular a number of steroids with a structure very similar to that of cortisone, including Kendall's compounds A and B and Reichstein's compound S, deoxycorticosterone acetate (DOCA) and hydrocortisone (Kendall's compound F) have been tested. Of all these only one, hydrocortisone, showed a similar enhancing effect on tuberculosis. This suggests that a high degree of chemical specificity is required to produce this biological phenomenon. All the present evidence indicates that these same chemical groupings are required to give relief in rheumatoid arthritis, for cortisone and hydrocortisone are the only active steroids. The possibility remained that those structurally similar steroids, which show no enhancement of stable murine tuberculosis, might antagonize the action of cortisone. A number of these "inactive"

RELATIONSHIP BETWEEN HOST CELL AND PARASITE IN TUBERCULOSIS

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steroids were administered concurrently with cortisone but none were antagonistic, neither were they synergistic.

Similar results have been obtained with cortisone in murine tuberculosis by Solotorovsky, Gregory & Stoerk (1951), who showed enhancement of an infection produced by an attenuated strain of *Mycobacterium tuberculosis* and also that cortisone counteracted the protective effect of previous vaccination.

Cortisone has been tried on tuberculosis in other species, including the rat, rabbit and guinea-pig. The rat, which is normally highly resistant to tuberculosis, developed an acute, diffuse and fatal infection when cortisone was given (Michael, Cummings & Bloom, 1950). Lurie, Zappasodi, Dannenberg & Cardona-Lynch (1953) concluded that, in the rabbit, while cortisone increased the number of tubercles and the number of tubercle bacilli within them, the size of lesions and the spread to the local lymph nodes was reduced, in pulmonary tuberculosis, following inhalation of tubercle bacilli. Greenburgh, Robson & Willcox (1953) were able to watch the effect of cortisone on the development of local corneal tuberculosis in the rabbit, using the technique originally described by Gardiner, Rees & Robson (1949). The hormone, administered from the start of the infection or delayed until the tubercle had developed, slowed the progress of the lesion although the number of tubercle bacilli was unaffected. Cessation of treatment was followed by a very rapid increase in size of the lesion. It seems less certain that cortisone exacerbates tuberculosis in the guinea-pig, for while Spain & Molomut (1950) and Coste, Pierre-Bourgeois, Galmiche, Vic-Dupont, Mollon, Nahel & Blatrix (1951) reported enhancement of the infection, LeMaistre & Tompsett (1951) and Winner & Evans (1952) were unable to show any adverse effects.

The other general action of cortisone is the depression of allergy and in particular its action on allergic hypersensitivity in tuberculosis. Using the response to intradermal tuberculin as a measure of hypersensitivity in the guinea-pig infected with *Bacille Calmette Guérin* (BCG), Long & Miles (1950) found that cortisone or adrenocorticotrophic hormone (ACTH) produced a definite though limited depression. More recently Long & Spensley (1954) tested a large number of steroids and found that only cortisone and hydrocortisone and their respective 21-monoacetates showed depression of tuberculin sensitivity. These same two steroids are the only ones showing therapeutic activity in rheumatoid arthritis as well as enhancement of experimental tuberculosis.

When the mechanism is considered by which cortisone, under certain conditions, enhances the susceptibility of some species to tuberculosis, it must be stressed that the hormone produces a similar effect with many other unrelated infections caused by bacteria, viruses, spirochaetes, trypanosomes, malaria parasites and fungi in many unrelated hosts. It is therefore most unlikely that a specific operative factor will be found for tuberculosis; certainly cortisone has no direct stimulating action on the growth of *Myco. tuberculosis* in vitro. On the other hand, cortisone has a general suppressive action on granulation tissue and on collagen formation in wound healing (Ragan, Howes, Plotz, Meyer & Blunt, 1949) and a suppressive effect on the local inflammatory response to infection (Cook & Smith, 1952) or to non-specific trauma (Bangham, 1951). It also causes lymphopenia and lymphoid atrophy (Antopol, 1950). This decreased response to inflammation or trauma is probably due to a protective action of cortisone on the arterioles and capillaries that counteracts the usually increased permeability and leucocyte migration (Ebert & Wissler, 1951). In a local tubercle, observed by the rabbit-ear chamber technique, Ebert (1952) noticed that cortisone, while profoundly reducing the degree of vascular damage, had no suppressive action on the degree of necrosis. This action of cortisone could easily be a double-edged weapon, for, while tending to isolate the infection from the rest of the body, it might prevent the arrival of cellular and humoral agents concerned with combating infection, and thus result in free multiplication of the parasite. The administration of cortisone to the mouse or rat with tuberculosis produces just this effect: a tremendous increase in the number of tubercle bacilli, which presumably increases the local necrosis. In the rabbit, although the tubercles may be smaller, with less local lymph-node involvement, they too usually contain more tubercle bacilli. The adverse effect in the guinea-pig is less certain but, when it occurs, is associated with larger and more caseous lesions. Gell & Hinde (1951) studied the cytological changes produced by cortisone in the tuberculin reaction in the skin of sensitized rabbits. They observed a marked reduction in the cellular reaction and in particular of the reticulo-endothelial mononuclear cells, caused by a decrease in infiltration of these cells from the outside. There was also a profound suppression of hyperaemia. The fact that cortisone did not suppress the general phagocytic activity of the macrophage (Gell & Hinde, 1953) suggests, indirectly, that failure of a cell to migrate may be due to a change in the environment rather than to direct damage to the cell. These altered environmental conditions might well be secondary to a direct action of cortisone on the local blood vessels.

From these studies with experimental tuberculosis it can be concluded that in some species of animals cortisone may definitely enhance the infection. The dosage of hormone required to bring about these changes is large, certainly far above physiological levels, and therefore most unlikely in itself to play a part in the natural development of experimental or human infections. On the other hand, the effective dosage of cortisone commonly used for man, although somewhat less than that used in experiments on animals, is also large. These findings should certainly be a warning of the possible danger of enhancing a known or unrecognized tuberculous infection by cortisone in man. What then is known about the effect of cortisone in human tuberculosis? Quantitative studies have shown that cortisone and ACTH reduce the response to tuberculin in sensitive subjects (Lovell, Goordman, Hudson, Armitage & Pickering, 1953); these results are almost identical with those obtained in the guinea-pig by similar methods (Long & Miles, 1950). A number of cases have been reported of acute generalized tuberculosis, following upon a course of cortisone, in patients who primarily had no recognizable disease. These have fortunately been rare, certainly when compared with the number of patients receiving the hormone. On the other hand, a more definite opinion can be given on the effect of cortisone in patients known to have tuberculosis. An analysis of 81 such cases treated with cortisone and/or ACTH showed that in 41 the infection was made worse, and in only 10 was the result favourable (American Trudeau Society, 1952). Recently in Great Britain, Houghton (1952) has reported on 10 cases of allergic reactions to streptomycin or *p*-aminosalicylic acid (PAS) in pulmonary tuberculosis treated with ACTH. The hormone

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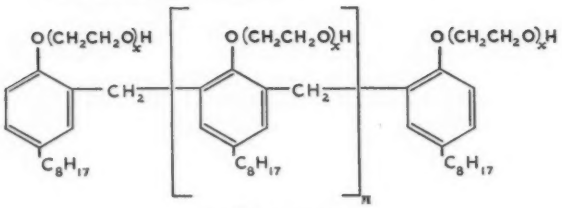
was given in combination with streptomycin and PAS and in all cases it suppressed the allergic reaction without adversely affecting the infection. While the final outcome of giving cortisone to a patient with tuberculosis may be very dependent on the exact conditions at the time of treatment, in general a drug that can profoundly suppress inflammation is a potential danger in any type of infection, particularly as the harmful effect may not become apparent until therapy with such a drug as cortisone is finished.

2. Antituberculosis Action of Certain Surface-Active Polyoxyethylene Ethers

In 1951, Cornforth, Hart, Rees & Stock, working at the National Institute for Medical Research, reported that certain non-ionic surface-active polyoxyethylene ethers produced a striking suppressive effect on the course of an acute tuberculous infection in the mouse. The observation originated from a study of factors influencing the susceptibility of mice to tuberculosis and in particular the part played by body lipids. A new technique of giving intravenous injections of a commercial non-ionic detergent, Triton A20 (Triton WR 1339), was tried following the report of Kellner, Correll & Ladd (1949) that these agents produced a prolonged and marked rise in the blood levels of cholesterol and phospholipids. Although associated with serious acute toxic effects, Triton A20 markedly inhibited the development of tuberculosis. An homologous series of non-ionic surface-active agents, similar in structure to Triton A20, was therefore synthesized (Cornforth *et al.* 1951). They were prepared by the action of ethylene oxide on an intermediate complex resinous mixture of *p-tert.*-octyl phenol formaldehyde condensation products. In this series the intermediates are primarily mixtures of linear polynuclear products. The general formula of this series is given in fig. 1 ; the mixture, D2, having various values of n from 0 upwards and an average of 20 units of ethylene oxide per phenolic nucleus, showed a chemotherapeutic activity similar to that of Triton A20, but was less toxic.

More recently, Cornforth, Hart, Nicholls & Rees (1954) have prepared an entirely new series of polyoxyethylene ethers from pure crystalline intermediates which probably belong to a group of macrocyclic compounds, the simplest of which is tetranuclear (fig. 2). Two such compounds (LOC and HOC) were prepared, with *p-tert.*-octyl phenol as the parent phenol. Atomic models showed that macrocyclic tetranuclear compounds could theoretically exist in four

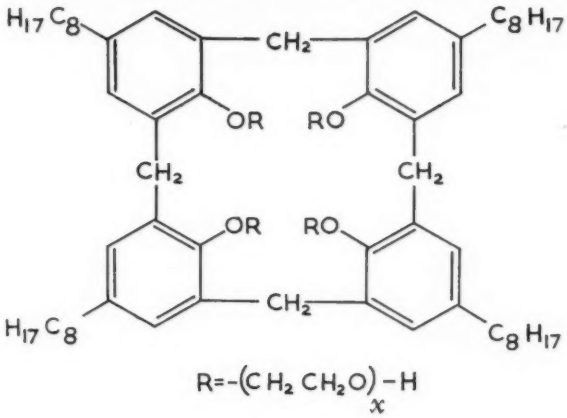
FIG. 1. CHEMICAL STRUCTURE OF THE LINEAR SERIES OF NON-IONIC SURFACE-ACTIVE POLYOXYETHYLENE ETHERS



$x = 20$ (average value)

In the chemotherapeutically active mixture (D2), $n = 0, 1, 2, 3$ and higher integers.

FIG. 2. EXAMPLE OF THE CHEMICAL STRUCTURE OF THE MACROCYCLIC SERIES OF NON-IONIC SURFACE-ACTIVE POLYOXYETHYLENE ETHERS



stereoisomeric forms and the authors considered that the two compounds isolated by them were probably isomers of that type. The two pure intermediates were condensed with ethylene oxide to form the corresponding surface-active agents (LOC–15, HOC–15, etc., the number indicating the average units of ethylene oxide). The average molecular weight of the macrocyclic surface-active agents, for example, HOC–20 or LOC–20, was 4,000. The linear and macrocyclic agents are both water-soluble.. In both series the octyl phenol moiety of the molecule constitutes the hydrophobic portion, while the hydrophilic portion is represented by the ethylene oxide chain. The balance of the water-attracting and water-repellent groups of the molecule accounts for their surface-active properties. Not only are these agents new chemical types of antituberculosis compounds but it is novel to have non-ionic surface-active properties associated with therapeutic activity.

The more general biological activities of these compounds have shown that the therapeutically active members of the linear and macrocyclic series are less toxic than the commercial product (Triton A20). Although the acute toxicity of these compounds is extremely low (LD_{50} greater than 2.5 g./kg. of body-weight by subcutaneous or intravenous administration), chronic toxicity tests have so far shown that all produce a certain amount of liver damage (sufficient to preclude their use in man). They are excreted slowly from the body, being present in the blood many hours and even days after a subcutaneous or intravenous injection. They are not absorbed when given by mouth. Like the commercial product many, though not all, of the members of these series produce some lipaemia, but this property varies considerably with the particular series and the ethylene oxide chain-length. For example, while all the derivatives of LOC with average ethylene oxide chain-lengths between 15 and 75 units produce marked lipaemia, the HOC compounds produce far less, giving only slight lipaemia with 15 units and none with 20 or more units.

The antituberculosis activity of these compounds was generally assessed by using a standard mouse test (Cornforth *et al.* 1951). By this test, D2, HOC–20 and LOC–20 showed a high order of activity, comparable to that obtained with

streptomycin. The therapeutic activity of these surface-active agents was very sensitive to changes in ethylene oxide chain-length. While the greatest activity for all three products was obtained with an average chain of 15–20 ethylene oxide units, an increase to 30 units, as, for example, LOC–30 or HOC–30, abolished activity. The therapeutic activity of D2 was confirmed in the guinea-pig, in which a substantial curative action was shown in an established tuberculous infection; but the effect was probably rather less than that obtained with a similarly infected group treated by streptomycin (Rees, 1953). Solotorovsky & Gregory (1952) have recently reported that Triton A20 acted synergistically with dihydrostreptomycin in a mouse infection.

These very promising in-vivo results may be contrasted with a lack of bacteriostatic action, since, at concentrations up to 2%, these agents did not inhibit the growth of tubercle bacilli in vitro. Some of them in fact facilitate submerged and dispersed growth. How do they work? Are they broken down or built up in the body to produce therapeutically active compounds ? Many experiments were undertaken to answer this important question but under no conditions has an inhibitory substance been detected in the blood from animals heavily treated with these compounds (Rees, 1953). Other tests were done to see whether there was any decrease in the virulence of tubercle bacilli grown in the presence of these surface-active agents or isolated from animals treated with these agents, but no such decrease was detected.

The lack of any demonstrable direct activity by these agents on the tubercle bacillus led to further consideration of their effect on the host. The most obvious and indeed the most dramatic change was lipaemia, with its associated rise in blood cholesterol and phospholipid levels, which occurred not only with Triton A20 but with D2 and the LOC compounds. More recently it has been possible to dissociate these effects from therapeutic activity, for while the therapeutically active compound HOC–20 produces no lipaemia, the LOC–20 and LOC–30 both produce lipaemia but only the former is therapeutically active. It was possible that the tubercle bacillus might be more readily phagocytosed by the macrophage and/or the polymorphonuclear leucocyte cell in the presence of these agents, but in-vitro and in-vivo tests have failed to show any such action.

One action of the therapeutically active agents, which is undoubtedly mediated through the host, is depression of tuberculin sensitivity. Hart, Long & Rees (1952) found that these agents produced a definite though limited depression of the tuberculin response in tuberculous and BCG-vaccinated guinea-pigs. The degree of desensitization was comparable to that produced with cortisone (see above), but the mode of action was different. The studies of these authors showed further that while the chemotherapeutically active representatives of the D2 series diminished tuberculin sensitivity, the inactive representatives did not. While this association suggests that the mechanism of the antituberculosis action and that of the depression of sensitivity may well have some common factor it seems unlikely that there is a causal connexion between the two effects.

Recently Mackaness (to be published) has shown that monocytes harvested from animals previously treated with the commercial agent (Triton WR 1339) become altered in some way so that tubercle bacilli that have been ingested by them are partially or completely inhibited in their growth, and are under certain conditions destroyed within the monocyte (the phagocytic activity of these monocytes was not increased). The addition of the same agent to the culture medium of monocytes isolated from normal untreated animals had no direct effect on the growth of intracellular tubercle bacilli. It must be stressed that the toxicity of these agents for the isolated monocyte limited the concentration (0.025%) used in these direct tests. Whether the monocytes become indirectly altered in vivo because of changes brought about in the tissues of treated animals or whether the surface-active agent can be taken up directly by the monocytes (and there act directly on the intracellular organisms) under the conditions existing in vivo but not under those existing in vitro remains as yet unproven. On the other hand, this work suggests the monocyte as a site at which the antituberculosis action of these agents could take effect in vivo.

The recent experimental work with cortisone and certain surface-active polyoxyethylene ethers, reviewed in this article, shows that it is possible to influence, by chemical means, the outcome of a tuberculous infection through the host rather than by a direct attack on the tubercle bacillus. This possibility offers a new experimental approach to the tuberculosis problem as a whole and to successful chemotherapy in particular. The antituberculosis polyoxyethylene ethers are chemically a very inert type of compound but they possess groups that are responsible for their powerful surface-active physical properties. The chemotherapeutic activity of these agents is almost certainly related, in some way, to their surface-active properties. It is possible therefore that other non-ionic surface-active agents, of relatively high molecular weight, but with different chemical structure, would show therapeutic activity. If this idea is confirmed, then a new type of antituberculosis agent, based on a physical rather than a chemical action, will have been established.

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RECENT DEVELOPMENTS IN CONTROLLED TRIALS IN PULMONARY TUBERCULOSIS

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Within the last few years an important advance in the field of pulmonary tuberculosis has been the development of the controlled trial as a method of assessing the effects of treatment. The technique has been applied particularly to the study of the use of chemotherapeutic substances. The same method is now being extended to the investigation of bed-rest, the various forms of collapse therapy, and resection.

There have been comparatively few reports dealing with the organization of controlled trials in tuberculosis; the earliest was in connexion with a trial of Sanocrysin undertaken by Amberson, McMahon & Pinner (1931). In 1944, Hinshaw & Feldman described the way in which they considered that controlled trials of chemotherapeutic substances in clinical tuberculosis should be undertaken. Subsequently, in 1946, the first rigorously planned investigation of the use of streptomycin with a concurrent study of controls was undertaken by the Medical Research Council (1948). This investigation established beyond question the importance of the controlled trial in pulmonary tuberculosis. Hart (1949) and Daniels (1951) lucidly discussed methods of conducting controlled trials, and Hill (1951) has forcefully enunciated their rationale. More recently, Tucker (1953) has presented a critique of some factors in controlled trials. At present the three largest organizations conducting these trials are the Tuberculosis Research Unit of the Medical Research Council (MRC) (under the direction of the Council's Tuberculosis Chemotherapy Trials Committee), the USA Veterans Administration, and the US Public Health Service. It is, however, most gratifying to see that in more and more individual units such studies are now being planned and undertaken.

The methods of conducting controlled trials continue to evolve. In the present paper some recent developments will be discussed and illustrated with particular reference to the current MRC trials of isonicotinic acid hydrazide (isoniazid) in pulmonary tuberculosis. The wide and ready acceptance of the findings of recent trials places great responsibility on those in any way connected with the planning, the co-ordination, the analysis of results, or the preparation of the report. If at any stage inaccuracy creeps in or a false assumption is made, the conclusions may be of uncertain reliability, or frankly unreliable. The reader should be in a position to assess the merits of the trial for himself. Hill (1951) stresses that " the whole plan and its working out should be laid before the reader so that he may see precisely what was done." But often the most fundamental points are left in doubt. There is frequently a failure even to make clear exactly what chemotherapy is under study. For example, the term PAS is loosely applied both to *p*-aminosalicylic acid and to its salts despite the considerable difference this makes in the dosage, for 12 g. of the acid are equivalent to 16 g. of the sodium salt. Such ambiguities cause much confusion in the literature.

1. Ethical Considerations

It is essential before undertaking any trial to be sure that its aims are entirely ethical, and that patients are not as far as can be known exposed to harm because they have been included. It is now generally accepted that, provided the treatments under study meet ethical requirements and there is a genuine doubt of their relative merits, then the random allocation of patients to the treatments is not merely permissible, but the only ethical way of investigating those merits. A clinician must, however, always be allowed the right to withdraw a patient from a trial if, because of deterioration in the patient's condition, he considers that it is unjustifiable to continue with the treatment allocated. In practice, if the

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aim of the trial has been carefully chosen and its conduct properly planned then the numbers of patients who have to be withdrawn for this reason will be very small.

Decisions as to what treatments are ethical depend on the treatments which are currently available to the population under study; they therefore vary from year to year and from country to country. In the original controlled trial of streptomycin in pulmonary tuberculosis (Medical Research Council, 1948), the effect of streptomycin and bed-rest was compared with that of bed-rest alone. The disease selected for study was acute, extensive, bilateral pulmonary tuberculosis of recent origin in young adults, a type for which at that time (1946) the only acceptable treatment available was bed-rest. The supplies of streptomycin in Great Britain were severely limited so that there was not enough for all the patients who might have been expected to benefit from the drug. It was therefore quite ethical to have a control group treated by bed-rest alone. Now that abundant supplies of antituberculosis drugs are available it is no longer ethical to have an untreated control group in the study of severe lesions, since these generally respond to chemotherapy. A control group is still quite ethical if it is doubtful whether the type of disease selected for study is affected by chemotherapy at all, for example, uncomplicated primary tuberculosis in children.

2. Design of Trials

Before any trial is embarked on, a protocol should be prepared. It should detail for the clinicians and bacteriologists, in a precise fashion, the objects of the trial, the type of case to be studied, the treatments to be allocated, and the routines of the clinical, bacteriological and pathological investigations that are to be followed. It cannot be stressed too strongly that a protocol is as essential for the small as for the large trial. It should not be left to chance that the necessary data will be forthcoming without precise planning.

a. Types of Controlled Trial

Controlled trials in pulmonary tuberculosis may be divided into three main classes : (i) the pilot trial; (ii) the limited type of trial; (iii) the large-scale trial.

i. *The pilot trial* is a small-scale trial undertaken in a single or at most a few hospitals. The object is to obtain basic information from which to decide whether a more elaborate and large-scale trial should be undertaken. Valuable information is often provided, particularly when a treatment is found to be unsuitable, for example, the USA Veterans Administration pilot studies of amithiozone (Schwartz & Salkin, 1952; O'Dell, Pitts, Rowan, Dye & Hughes, 1952). Pilot trials carry the risk that suggestive results in favour of a treatment may be obtained and accepted without a confirmatory study being undertaken on a scale large enough to establish them adequately. Also the planning and control of these studies is sometimes rather haphazard, presumably on the grounds that they are only " pilot ".

ii. *The limited type of trial.* The first three trials of chemotherapy in pulmonary tuberculosis conducted by the MRC (Medical Research Council, 1948, 1950, 1952a), in common with pilot trials, were all comparatively small. They did, however, give a clear-cut evaluation of the treatments under study by meticulous planning and execution and by limiting the study to an uncommon but very suitable type of case for assessing the response to chemotherapy, namely, acute, progressive, bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved, unsuitable for collapse therapy, age-group 15 to 30. It should be added, however, that since the conclusions were obtained from a study of a particular type of acute disease they did not necessarily apply to other forms, such as minimal or chronic lesions.

iii. *The large-scale trial.* Large-scale trials are difficult to organize and take up a great deal of the time of co-operating clinicians and bacteriologists. They should therefore not be embarked on lightly. Provided that some basic information is available about the drug to be studied, it may be possible to start the trial without the delay required for a preliminary pilot trial. A rapid start may also be highly desirable, as with isoniazid. The earliest reports (Robitzek, Selikoff & Orstein, 1952; Grunberg & Schnitzer, 1952) were very promising. The drug was cheap, readily available, and without obvious toxicity. It received great publicity in the daily press, and there could have been no doubt that it would be widely used. It was thus essential to obtain information on its value quickly so that guidance could be given to the profession in its use. Delay in starting a trial would also have made it difficult to obtain patients who had not already received the drug. It was against this background that the large-scale trials were planned on both sides of the Atlantic. In the MRC trial (Medical Research Council, 1952b, 1953a, 1953b, 1953c), a large number of hospitals throughout Great Britain (eventually numbering 53) co-operated. To increase the rate of intake a wider range of types of disease was studied than in the earlier MRC trials. The number of patients admitted grew rapidly. Within a month over 200 patients were under study; by 10 weeks 500; and when the admission of new cases to the trial was stopped, a little over 18 months after the start, some 1,400 patients had been admitted to the study.

The large-scale co-operative trial does not lend itself readily to the detailed study of individual patients, particularly if this involves the use of special facilities, not generally available. Within a large-scale trial, however, individual units may make special studies. Thus in the current MRC trial some units undertook renal and liver function tests, and others, detailed haematological studies. Valuable additional reports may appear from individual units (Crofton & Mitchison, 1948). Indeed the small intensive trial undertaken by even a single hospital has an important place.

b. Importance of Adequate Numbers

Bentley (1936) has referred to drawing conclusions from too few cases as one of the seven deadly sins which all investigators must avoid. This applies most forcefully to controlled trials. The number of patients needed depends on the magnitude of the differences in effectiveness which exists between the treatments under study. If these are small, then several hundred patients may be required to demonstrate a definite superiority of one of the treatments. If they are large, many fewer will suffice. The type of lesions selected for study is very relevant since acute extensive disease lends itself more readily to assessment than do limited or chronic lesions. It has already been pointed out that restriction of the earlier MRC trials to a specially selected form of acute disease made it possible to obtain clear-cut results from as few as 100 patients. Even smaller numbers may be adequate for a study of the value of a drug in delaying the emergence of drug-resistant bacteria. Thus

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information on the importance of initial PAS resistance was obtained by comparing groups of 12 and 10 patients with the common characteristic that all had had at least one month's treatment with PAS alone (Medical Research Council, 1953b). Nevertheless, the investigator must always make sure that the data are sufficient to bear the weight of any conclusions drawn.

c. Role of the Statistician

The co-operation of a statistician is essential at every stage of a trial no matter what its size, from the formulation of the plan to the preparation of a report. The complex large-scale trial with its increased tempo of analysis and reporting has further accentuated the importance of a close partnership between doctor and statistician, both of whom must have an intimate knowledge of the data.

d. Random Allocation of Patients to Treatment Groups

When a controlled trial is undertaken it is fundamental to allocate the cases to the different treatments under study in a random manner, that is, in a way that avoids the possibility of bias, whether conscious or unconscious. It is essential that the method of random allocation should give a clinician no chance of knowing in advance which of the treatments under study a patient will receive if he is admitted to the trial.

e. The Choice of Treatments for Study

A new form of antituberculosis chemotherapy raises many problems, but the most important issue is to compare it both clinically and bacteriologically with the previous most effective combination. Such an assessment carries a major defect. If the effectiveness of the new drug when given alone is well below that of the previous most effective combination, it may prove impossible to say whether the benefit that patients being treated by the new drug receive is greater than might be expected from bed-rest and a placebo. Further assessments must therefore be introduced. This can be done by undertaking, preferably from the start, an additional study of the clinical and bacteriological effectiveness of the new drug when administered together with one of the two drugs of the best previously available combination. Thus in the MRC isoniazid trial, three treatments were studied from the outset, namely, isoniazid alone (200 mg. daily), streptomycin (1 g. daily) plus sodium PAS (20 g. daily) which was the best combination previously known, and streptomycin (1 g. daily) plus isoniazid (200 mg. daily). In this way not only was isoniazid alone compared with streptomycin plus PAS but, in addition, a clinical and bacteriological comparison of streptomycin plus isoniazid with streptomycin plus PAS was made. The finding that streptomycin plus isoniazid was more effective clinically than streptomycin plus PAS (Medical Research Council, 1953a) was evidence that isoniazid was an antituberculosis agent of definite activity. The introduction of streptomycin plus isoniazid also permitted a study of the relative efficacy of isoniazid and PAS in preventing the emergence of streptomycin-resistant organisms; this particular assessment is referred to again later.

f. Concurrent Comparisons

Except in very special circumstances it is essential, when comparing treatments, to restrict the comparison to patients admitted to the trial concurrently. This point needs stressing particularly in connexion with the recent large-scale trials in which new combinations have been introduced for study in the later stages.

A study of the cases in the current MRC trial of isoniazid has revealed that the patients admitted in the later phases of the trial had on average much more recently diagnosed disease than those admitted to the earlier phases. It would therefore not be legitimate to compare patients receiving PAS plus isoniazid, a treatment allocated in the last phase of the trial, with the patients allocated isoniazid alone or streptomycin plus PAS over a year earlier, when the trial had just commenced. Too often retrospective comparisons are made without first establishing that they are justified.

g. Retrospective Comparisons

Provided that great care is taken, it is sometimes permissible to undertake retrospective comparisons, as was done in a series of three MRC chemotherapy trials in pulmonary tuberculosis carried out between 1946 and 1951 (Daniels & Hill, 1952).

The retrospective comparisons were possible because:

i. The type of case under study was carefully defined and the definition was strictly adhered to throughout all three trials.

ii. All cases were submitted to a central panel of clinicians, with permanent members, who decided from the history and radiographs that the criteria for admission had been satisfied.

iii. Random allocation was rigid.

iv. A careful analysis was made of the clinical and radiographic features of the patients on admission to the trials. This established that the groups of patients in the different treatment series had disease of comparable severity.

v. The first and second trial had one treatment in common, namely, daily administration of streptomycin. The second and third trials also had a common treatment: daily streptomycin (1 g.) plus sodium PAS (20 g.). This use of a " link " treatment confirmed that the response of the groups of patients on the same treatment was the same in successive trials, and thus further strengthened the case for a comparison between the treatments in all the three trials.

h. Previously Treated Patients

The response of patients to a second or subsequent course of chemotherapy is, in general, less satisfactory than that of patients receiving their first course. This is true even when there is no evidence that the organisms are drug-resistant. It follows that patients who have received a previous course of chemotherapy should preferably be studied separately; if they are included with patients receiving a first course of treatment, it is important to ensure that the percentage of patients who are receiving a second course of treatment is similar in each treatment series.

3. Assessment of Results

a. Assessment of Patients on Entry

When a patient is admitted to a trial it is essential to arrange an initial period of observation and investigation before the commencement of the prescribed treatment. In this period clinical, pathological and bacteriological assessments are undertaken, and these establish a base-line from which all subsequent progress can be measured. It also permits the effectiveness of random allocation to be tested.

b. Testing the Effectiveness of Random Allocation to Treatment Groups

Before the treatments are compared, it is important to establish as far as possible whether the random allocation has succeeded in dividing the patients into comparable groups. This may be done by studying a series of factors relevant to the outcome of treatment, such as age, degree of lung involvement, size of cavitation, general condition, level of pyrexia, erythrocyte sedimentation rate, on admission to the trial. If several of these factors are studied and the groups of patients are found to be comparable, it is then safe to assume that the groups are comparable in respect of all other relevant factors, known or unknown. If some difference is observed, say, that the patients in one group are initially more ill, then allowance can be made for this in the interpretation of the results.

c. Assessment of Treatments

There is general agreement on the factors that should be studied in order to compare the merits of treatments in a trial. They are:

i. The relative clinical effectiveness of the treatments.

ii. The incidence of sputum negativity.

iii. The emergence of drug-resistant strains of bacteria.

iv. Toxicity of the drugs.

It is on these factors, in addition to the ease and convenience of administration, palatability and cost, that the choice of a treatment for a patient will depend. A trial must therefore be planned to give the maximum information about these factors.

There still remain considerable differences of opinion on the short-term assessment of clinical effectiveness. Some authorities ignore all factors except radiographic change, objectively assessed, relying on this and the bacteriological data. In addition to these, the analysis of the results of MRC trials always gives due consideration to resolution of pyrexia, lowering of the erythrocyte sedimentation rate, gain in weight, and, although this is a subjective criterion, to the physician's assessment of change in general condition.

The value of these latter factors was fully established in the MRC trial of isoniazid, which was organized so that regular monthly progress reports were obtained on every patient and analysed centrally. This central analysis ensured standardization of the data and permitted a continual review of the results. Within six weeks of starting the trial, an analysis of all the clinical features in over 100 patients who had been under treatment with streptomycin plus PAS or with isoniazid alone for a month had been undertaken together with a comparison of provisional radiographic assessments by the clinician in charge of each patient. From then on it was possible to reassure co-operating clinicians that isoniazid appeared to be of the same order of effectiveness as streptomycin plus PAS, and week by week this was confirmed on larger numbers and over a longer period of observation. The importance of this feature of the organization of the trial in ensuring the close co-operation of the large number of physicians cannot be stressed too greatly.

There is no major difference of opinion on the factors to be studied for a long-term assessment of treatment, the most important being survival rates, arrest of the disease, and the ability of the patient to resume full activity or employment.

d. " Therapeutic Targets "

In two recent trials comparing streptomycin and dihydrostreptomycin (Cohen, Johnsen, Lichtenstein & Lynch, 1953; Mahady, Armstrong, Beck, Horton & Lincoln, 1953), a new method of assessing treatments has been introduced. In these studies the medical staffs established one or more therapeutic objectives for each patient at the time of admission, for example, " To obtain maximal roentgenographic clearing " or " To effect maximal improvement of a complicating tuberculous lesion " or " To permit the use of definitive surgery " (Mahady *et al.* 1953). At the end of the trial an assessment was made of the degree of success achieved, using one of the terms " complete ", " partial ", " slight " or " failure ". Thus in effect, ill-defined therapeutic aims were set up, and somewhat vague assessments of the degree of attainment of these aims were made. In a field whose purpose is objective assessment, it is doubtful whether this innovation constitutes an advance.

e. " Blind " Clinical Assessments

The value of keeping the clinician uninformed as to which treatment each individual patient is receiving is well recognized. It enables a clinician to assess progress without being influenced by a knowledge of the treatment. This " blind " technique has not been generally applicable to tuberculosis since it would have entailed the administration of treatments simulating daily streptomycin injections or the large doses of oral PAS or both. In at least one trial of PAS therapy, however, the control patients received a placebo " of the same appearance, smell, and acid taste as PAS granulate " and in similar dosage, the clinicians being unaware which treatment had been allocated (Swedish National Association against Tuberculosis, 1950). In the two recent trials referred to above, which compared streptomycin with dihydrostreptomycin (Cohen *et al.* 1953; Mahady *et al.* 1953), the treatments were given blind. This was possible because of the similar character and route of administration of the two drugs. The result was a more objective clinical assessment of the toxic effects on vestibular and auditory functions, a very important point. A blind technique has also been used in trials of isoniazid alone (Joiner, MacLean, Pritchard, Anderson, Collard, King & Knox, 1952; Eggen, Klingenberg, Refsum, Tuxen & Ustvedt, 1953). With the likelihood that further new oral drugs of small bulk—such as isoniazid—will be developed, this method may well find a much wider application in tuberculosis.

f. Patients Removed from the Trial

The reasons for removing a patient from a trial must be carefully recorded, together with the treatment the patient was receiving and also the length of time that the patient was in the trial. Removals may be completely unconnected with the chemotherapy, as in some instances of discharge against medical advice. On the other hand a patient may take his discharge owing to dislike of a treatment, for example, streptomycin injections. The cessation of treatment due to toxicity is often a clear-cut failure of treatment. It may, however, especially when a new drug is under study, be uncertain whether a particular complication is a toxic manifestation or not, for example, haemoptysis during isoniazid therapy. Adequate details about removals should be reported to

enable the reader to decide on these and similar points for himself. Finally, a high incidence of removals may so interfere with random allocation that the series no longer remain comparable, and this may wreck the trial.

It follows that a controlled trial of a treatment in doses which are likely to give a high incidence of toxicity should not be undertaken, and experimentally high dosages are therefore unsuitable. It would be wiser to postpone the trial until it has been established that the proposed dosage can be tolerated.

The removal of patients may become particularly serious in long-term chemotherapy studies. Some idea of the relation of the numbers of removals to the duration of the study can be obtained from the current US Public Health Service trials. In that organization's first isoniazid study 12% of 390 patients had deviated from the prescribed chemotherapy by 20 weeks (Mount & Ferebee, 1953a); by 28 weeks the figure was 18% of 793 patients (Mount & Ferebee, 1953b) and by 40 weeks 26% of 791 patients (Mount, Jenkins & Ferebee, 1953). These figures clearly demonstrate a serious problem in planning controlled studies of chemotherapy for one or more years, as advocated by many clinicians. In the second study from the same organization (United States Public Health Service, 1954), 27% of 461 patients had departed from the prescribed chemotherapy by 20 weeks. This figure, high compared with 11% at 20 weeks in the earlier study, was undoubtedly related in part to the inability of patients to tolerate isoniazid in dosages of 10 mg./kg. of body-weight per day, a dosage which was being administered in three out of five regimes in the later study.

g. Deaths

In every type of trial the fullest details of all deaths should be obtained, together with the post-mortem findings. It is so important to establish the exact cause of death that the trial protocol should recommend autopsy for all fatal cases. The report should give a clear statement of the cause of death in each fatal case, the duration of treatment and also the therapy prescribed. A death may well represent a serious failure of treatment. However, if a gravely ill patient dies within a few days of starting treatment it would usually be unfair to consider this a failure of chemotherapy; even so, the fact must be recorded. On the other hand, in one recently reported chemotherapy trial (Cohen *et al.* 1953), the nine patients who died were excluded from the analysis on the grounds that they did not complete the prescribed four months' treatment. Moreover, the chemotherapy that each patient received was not recorded. This represents a major defect in the report.

h. Radiographic Assessment

The most valuable single factor in measuring a patient's progress is the assessment of radiographic change. In order to obtain strict objectivity in this assessment the interpretation of the radiographic series should be undertaken by an independent radiological assessor unaware of the treatment in any case. It is not adequate to accept assessments by the individual clinicians in charge of the patients, relying on an occasional check by an independent reading.

The assessment of radiographs of patients in a large-scale trial presents a major problem. It may be necessary to obtain an assessment of the serial radiographs of several hundred patients in a short space of time in order that they may be returned speedily to the centres to avoid interference with, or delay in, treatment. Since panel readings are exceedingly difficult to organize at short notice, the radiographic changes in the MRC isoniazid trial have been read by a single radiological assessor. This was adequate since the primary object of the trial was to obtain a comparison between treatments and not to establish absolute values of radiographic change. An alternative solution is to take duplicate x rays at each month for every patient so that one series becomes the property of the central organization. This is expensive and not generally practicable. The practice of undertaking panel readings on the spot by clinicians who may know the cases intimately is very undesirable, since the elimination of bias cannot be ensured.

Sessions for x-ray reading should be so planned that approximately equal numbers of radiographic series of patients on the different treatments are read at each session. In this way the inevitable slight variations in the standards of the assessor from session to session will affect all treatments equally. A high standard of radiography is important and the assessment should be undertaken on full-plate negatives. Positives and miniature radiographs, whether 5 in. × 4 in.[1] or the 70 mm. size, should be forbidden by protocol.

4. Bacteriology

a. Analysis of Data

In large-scale trials, the frequency with which bacteriological examinations are performed varies not only from centre to centre but also between the different treatments. Even in a single centre one treatment may be studied especially intensively. It is very important when analysing bacteriological data to ensure that no apparent advantage or disadvantage accrues to a particular treatment merely because numerous or few examinations have been undertaken on those patients allocated to it.

When a comparison is being made of the bacteriological features of treatments, the data may be presented for each period of a month. Alternatively, they may be presented as the results obtained at the end of each month; this can be done by restricting the analysis to data obtained within the period of a stated number of days on either side of the last day of each month's treatment. Of the two methods of presentation the latter is preferable since it gives results after the passage of a more accurately defined period of time, a primary point of study in all trials.

b. Importance of Initial Bacterial Resistance

In planning a trial it is very important to differentiate between patients with initially drug-resistant bacteria and those with initially drug-sensitive bacteria, since the latter may be expected to respond to chemotherapy better than the former. Hence, sensitivity tests should be performed on pre-treatment cultures made from all patients, and patients found to have had drug-resistant strains initially should be analysed separately. Unless these cases are so excluded, misleading conclusions may be reached. In the current MRC isoniazid trial an unexpectedly high incidence of bacterial resistance to streptomycin developed in patients receiving

[1] 1 in. = 2.54 cm.—Ed.

streptomycin plus PAS, and this combination appeared, at first sight, inferior to streptomycin plus isoniazid in delaying the emergence of streptomycin-resistant bacteria. When, however, PAS-resistance tests were undertaken on pre-treatment cultures of patients in the group receiving streptomycin plus PAS, it was found that the majority of patients who had developed streptomycin-resistant strains had had initially PAS-resistant strains and so were at a disadvantage from the start. When these cases were excluded from the main analysis, streptomycin plus PAS was found to be of the same order of effectiveness as streptomycin plus isoniazid in preventing the emergence of streptomycin-resistant strains of bacteria. A sub-analysis was then undertaken of the patients receiving streptomycin plus PAS who had received a month or more of treatment with PAS alone at any time previous to the trial, some of whom had PAS-sensitive strains, others PAS-resistant strains. This gave clear-cut evidence that streptomycin-resistant strains of bacteria emerged more readily in patients who had PAS-resistant strains initially, than in those who had PAS-sensitive strains initially (Medical Research Council, 1953b). Thus the development of streptomycin resistance under treatment with streptomycin plus PAS was related not to the administration of a previous course of PAS alone, but to the occurrence of PAS-resistant strains of bacteria.

A trial of a chemotherapeutic combination in patients, some of whom have sensitive bacteria, and others bacteria resistant to one or other drug, can give only limited and confusing results. In some trials in the USA the study of patients with drug-resistant strains has been undertaken by admitting patients known to have drug-resistant organisms to special treatment series. Such trials can yield very valuable information but care must be taken in planning them since difficult ethical issues are raised as to what combinations of drugs may justifiably be studied.

c. Objective Assessment of Bacterial Sensitivity

In the US Public Health Service Cooperative Investigation of isoniazid a further advance has been the introduction of an objective assessment of bacterial sensitivity (United States Public Health Service, 1953). In that trial, a culture made before treatment and a culture at 40 weeks from every patient were tested for bacterial resistance at a central laboratory in the absence of any knowledge of what drug or combination of drugs each patient was receiving; in addition cultures at four-week intervals from a sample of the patients were also tested centrally. This blind technique introduces an objectivity comparable to that of the independent radiographic assessment. Ideally the technique should be applied to all the monthly cultures from every centre instead of a sample, since combined chemotherapy gives such a high incidence of sputum negativity that fewer and fewer sensitivity tests can be undertaken (and the results become of correspondingly greater importance) as each month passes. Thus in the current MRC trial, after three months' treatment there were only 68 positive cultures from 219 patients receiving streptomycin (1 g. daily) plus sodium PAS (20 g. daily), and only 26 positive cultures from 120 patients receiving streptomycin (1 g. daily) plus isoniazid (200 mg. daily) (Medical Research Council, 1953b). A possible compromise in the study of combined chemotherapy would be for the central laboratory to perform sensitivity tests on a sample of, say, 1 in 5 cultures at one month, 1 in 3 at two months and then on every positive culture from three months onwards, always without knowledge of the treatment of each patient. These tests would be undertaken in addition to the routine monthly tests in the laboratory of each co-operating unit.

5. Conclusions

Large-scale controlled trials, far from being slow and unwieldy, have demonstrated that they can yield clear-cut information on a new form of antituberculosis chemotherapy in a remarkably short space of time. Contrast the information obtained on isoniazid in a period of little more than 18 months with the conflicting and unestablished opinions expressed over a period of 15 years concerning the value of gold therapy. In this short period controlled trials have demonstrated that isoniazid alone is a very effective agent in the treatment of pulmonary tuberculosis but that the incidence of the development of drug resistance is very high (Medical Research Council, 1952b, 1953b; United States Public Health Service, 1953; Dye, 1953); that this incidence is greatly reduced by combining isoniazid with streptomycin (Medical Research Council, 1953a; United States Public Health Service, 1953; Dye, 1953) or with PAS (Medical Research Council, 1953c); that both of these combinations are clinically very effective, especially daily streptomycin (1 g.) plus daily isoniazid (200 mg.), which may well be the most effective combination of two drugs yet available (Medical Research Council, 1953a); that increasing the dosage of isoniazid to 10 mg./kg. of body-weight per day in combined chemotherapy increases toxicity but not the clinical effectiveness (United States Public Health Service, 1954); that clinically over a period of 20 weeks a combination of all three drugs is probably not superior to a combination of streptomycin plus isoniazid or PAS plus isoniazid (United States Public Health Service, 1954); that general reversion of isoniazid resistance does not occur over a three-month period after treatment with the drug is stopped (Medical Research Council, 1953b). Truly this is a remarkable and fruitful yield for so comparatively short a period of study, and a great deal of data from the large-scale trials has still to be analysed, especially that concerned with the long-term effects of the treatments.

Hinshaw (1953) states that " Cooperative clinical research as applied to problems of tuberculosis therapy have been so eminently successful, regardless of the sponsoring agency, that other fields of clinical research should take more cognizance of this as a means to advance knowledge ". These controlled trials offer remarkable evidence of the willingness of clinicians and bacteriologists to co-operate in a trial by following regimes of treatment and observation set out in a protocol and by submitting their results for central analysis and reporting.

The dissemination of the results of the trials is obviously vital. Of equal importance is the spreading of knowledge of the techniques of conducting controlled trials, and this is the responsibility of all who organize them. It is the practice of the Tuberculosis Research Unit of the Medical Research Council to make freely available the protocols and other practical details of the trials to anyone who wishes to study them. In this way it is hoped to encourage and aid the development of this important and growing field of clinical medicine.

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PROBLEMS OF DRUG RESISTANCE

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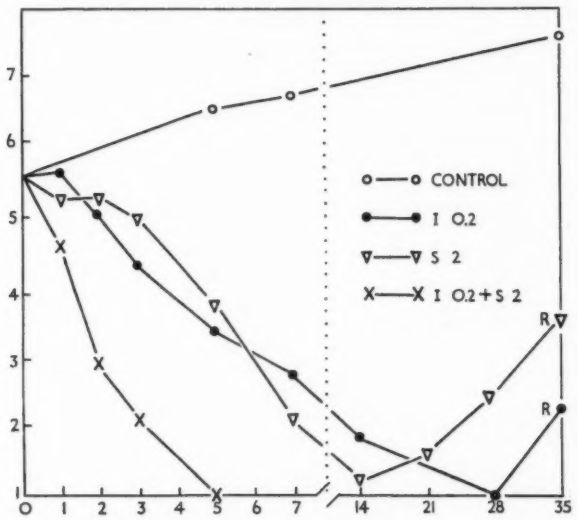
The three chemotherapeutic drugs in common use for the treatment of tuberculosis are streptomycin, isonicotinic acid hydrazide (isoniazid) and *p*-aminosalicylic acid (PAS). Strains of tubercle bacilli isolated from a patient after treatment with one of these drugs frequently require a higher concentration of the drug to inhibit their growth than did strains isolated before treatment. Such strains are said to have developed resistance. The subjects now to be discussed are the origin of resistance, its measurement and its significance during treatment with these drugs used either alone or in combination. The amount of work that has been carried out on these questions is very large and, of necessity, the views and evidence quoted are both controversial and highly selective.

1. Origin of Drug Resistance

There are two methods by which resistance may appear. In the first place any sensitive strain of tubercle bacilli contains a few organisms which are naturally resistant, sometimes to high drug concentrations. They have arisen by a process of mutation and are called mutants. It is important to realize that mutants resistant to one of the drugs are different bacilli from mutants resistant to another drug. The origin and types of mutants are discussed more fully elsewhere (Mitchison, 1953b). When this population comes into contact with therapeutic concentrations of either streptomycin or isoniazid the sensitive bacilli are killed, whereas the few resistant mutants can multiply and eventually constitute the whole strain, as is shown in curves S 2 and I 0.2 of fig. 1. During the periods represented by the left-hand descending portions of these curves the sensitive bacilli are being killed and the resistant mutants are growing, but still form only a small part of the population. During the periods shown by the right-hand ascending parts of the curves the multiplying resistant bacilli are becoming sufficiently numerous to cause the increases in the total viable populations. Since resistance develops during a single period of growth this process is called single-step selection.

FIG. 1. THE BACTERICIDAL ACTION OF STREPTOMYCIN AND ISONIAZID, ALONE AND IN COMBINATION (adapted from Singh & Mitchison, 1954)



Abscissae: period of incubation (days)
Ordinates: $\log_{10}$ viable units/ml.

The drugs were added to cultures of H37Rv in Tween-albumin medium and at intervals viable counts were made to determine the number of surviving viable units, i.e., clumps of one or more bacilli.
Streptomycin was added in concentrations of 2 units/ml. (S 2). Isoniazid was added in concentrations of 0.2 μg./ml. alone (I 0.2), and in combination with streptomycin (I 0.2 + S 2). A control culture contained no drugs.
R indicates that the strain was found to be resistant at the end of the experiment.
(The unit of streptomycin is defined in such a way that it is equivalent to the activity contained in 1 μg. of pure streptomycin base.)

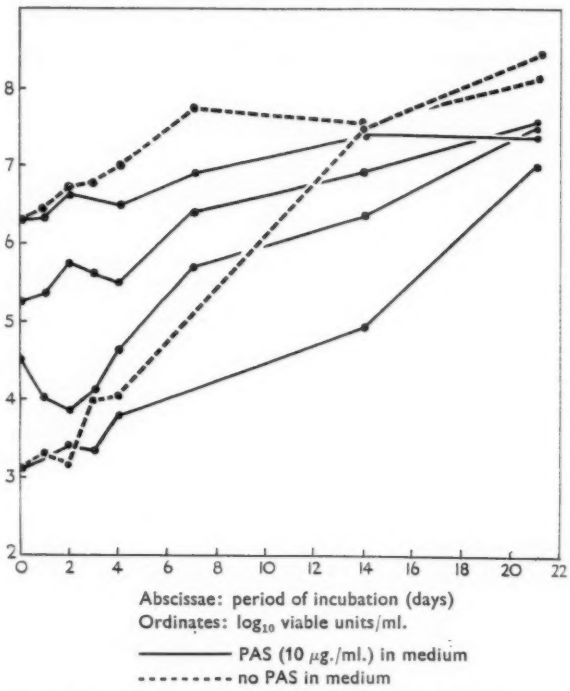
On the other hand, within the bacterial population there may be bacilli with resistance only slightly greater than the remaining sensitive organisms. During growth in subbacteriostatic concentrations of the drug these slightly resistant bacilli will be selectively encouraged. If, during successive periods of growth, the drug concentration is gradually increased, resistant strains will arise by a process of multiple-step selection. (Perhaps resistance may also be induced by contact with the drug, but this does not alter the argument.)

In the case of streptomycin both methods can occur in vitro. Mitchison (1953b) has suggested, from a study of different types of resistant strains of *Bacterium coli* and tubercle bacilli, that single-step selection is the predominant mechanism in patients; fig. 1, which represents this mechanism in vitro, thus represents also the mechanism in vivo. Isoniazid has many similarities to streptomycin and one assumes

that resistance to these two drugs develops in an analogous manner.

Although streptomycin and isoniazid are bactericidal, PAS is thought by Sievers (1949) and Desbordes (1952) not to inhibit growth until there has been an initial period of multiplication, the length of which is probably determined by the PAS concentrations. When the concentration of PAS is low (10 μg./ml., Nilsson, 1953), sufficient multiplication may take place during this period to allow even small inocula of bacilli to become slightly resistant by the process of multiple-step selection, after which they grow slowly. This is shown in fig. 2 which is taken from Singh & Mitchison (in preparation). In higher concentrations (100 μg./ml.) there is insufficient multiplication of small inocula to allow resistance to occur and the PAS is then bactericidal. However, it again fails to be bactericidal and allows resistance to develop when in contact with large numbers of sensitive bacilli.

FIG. 2. ACTION OF A LOW CONCENTRATION OF *p*-AMINOSALICYLIC ACID (PAS) (10 μg./ml.) WITH VARYING INOCULUM SIZES OF H37Rv (Singh & Mitchison, in preparation)



The technique used was the same as that described for fig. 1. At the end of the experiment all the strains that had been in contact with PAS were resistant to it.

2. Statistical Concept of Resistance

a. Sensitive Strains

Strains of human tubercle bacilli that have never come into contact with streptomycin, PAS or isoniazid (pre-treatment sensitive strains) have a remarkably uniform sensitivity to these drugs. The results of tests of sensitivity to streptomycin and PAS on such strains is shown in fig. 3. These tests were carried out by the Medical Research Council (1948b, 1953b) method in Tween-albumin liquid medium. The results are expressed both in terms of the minimal inhibitory concentration and of the resistance ratio, i.e., the ratio between the minimal inhibitory concentrations for the test strain and for the sensitive laboratory strain, H37Rv, which had been tested at the same time. As far as can be detected by these tests, all pre-treatment strains have an identical sensitivity to streptomycin (Mitchison, 1949) and probably an identical sensitivity to PAS (Mitchison & Monk, in preparation). The apparent variations shown in fig. 3 appear to be due to experimental error.

In the case of isoniazid no comparable data are available since, in all major trials, sensitivity tests have been performed on solid media, in which an accurate titration of the minimal inhibitory concentration was not carried out. However, where such titrations have been performed on small samples of strains (Mitchison, 1952; Rist & Grumbach, 1952; Rist, Grumbach, Cals & Riebel, 1952), all the results suggest that there are again no appreciable differences between the real pre-treatment sensitivities of different strains.

Some bovine strains seem to be naturally resistant to PAS (Djang, Bogen & Will, 1952) but sensitive to streptomycin and isoniazid.

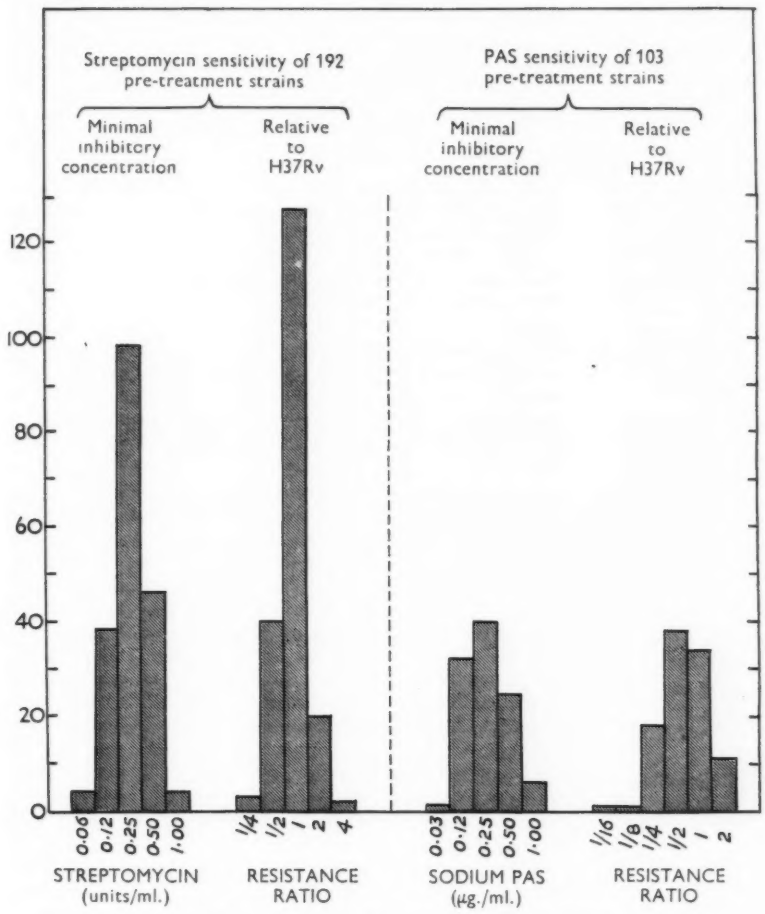
b. Resistance

A resistant strain has been defined as one requiring a higher drug concentration to inhibit growth than does a pre-treatment sensitive strain from the same patient. Since all pre-treatment strains have the same real sensitivity, the distinction between a sensitive and a resistant strain can be obtained from a distribution of the sensitivities of pre-treatment strains from different patients, such as is illustrated in fig. 3. A resistant strain is one whose sensitivity falls outside the limits of such a distribution, and definitions of resistance based on this principle have been adopted in MRC publications (Medical Research Council, 1953b).

The distributions shown in fig. 3 were prepared from tests carried out in one laboratory. A definition of resistance could have been obtained from these with the same accuracy, in terms either of a limiting absolute concentration or of a limiting resistance ratio. However, tests carried out in other laboratories might vary slightly, say, in the composition of the medium or in the size of the inoculum. Such differences would be expected to alter the limiting absolute concentration separating sensitive from resistant strains, but would not alter the limiting resistance ratio, since they would affect the test strain and the standard strain, H37Rv, to the same extent. Thus, to detect the lowest degrees of resistance with reliability in different laboratories, one must titrate accurately over the range of concentrations suitable for measuring the sensitivity of strains which are sensitive or of low resistance. Accurate titrations of highly resistant strains are not necessary. One must also include a standard sensitive strain in every batch of tests and define resistance in terms of a resistance ratio.

In many investigations, particularly those in which solid medium sensitivity tests are used (American Trudeau Society, 1952), strains are classified as sensitive or as of various grades of resistance according to their growth in the presence of arbitrary, widely spaced drug concentrations. This will

FIG. 3. STREPTOMYCIN AND *p*-AMINOSALICYLIC ACID (PAS) SENSITIVITY OF PRE-TREATMENT CULTURES (Medical Research Council, 1948b, 1953b)



Ordinates: number of cultures of *Myco. tuberculosis*

mean that an unknown proportion of strains of low resistance will be classified as sensitive and sometimes a few sensitive strains may be classified as resistant or of doubtful resistance. Such a procedure may be satisfactory in the first analysis of the emergence of resistance during treatment with one drug alone, as in the technique for measuring isoniazid resistance (Medical Research Council, 1953b) used in the MRC trials of isoniazid (Medical Research Council, 1952b). It is unsatisfactory in circumstances to be described later (section 7).

3. Development of Resistance during Treatment with a Single Drug

The percentage of patients with acute pulmonary tuberculosis who have developed resistant strains after three months is shown in Table I, the figures being taken from MRC trials (Medical Research Council, 1950, 1953c). The type of disease in each group of patients is comparable. One can conclude that resistance to streptomycin and resistance to isoniazid emerge at about the same speed, but that resistance to PAS develops more slowly.

Two factors will tend to determine whether resistance emerges in individual patients: first, the total population of bacilli before treatment is begun, since the larger the population the greater the number of resistant mutants present; second, whether conditions are favourable for the growth of these few resistant bacilli. In tuberculous meningitis[1], streptomycin resistance develops less often than in pulmonary tuberculosis. This is most likely to be due to the population of bacilli in the meninges being so small that it seldom contains resistant mutants. In patients with pulmonary tuberculosis, streptomycin resistance emerges most rapidly and to the highest degree in those who are the most ill at the start of treatment (Bignall, Clegg, Crofton, Smith, Holt, Mitchison & Armitage, 1950; Medical Research Council, 1948a, 1950). This is presumably due to the large bacterial population and to an inadequate defence mechanism in these patients.

4. Significance of Resistance during Treatment with a Single Drug

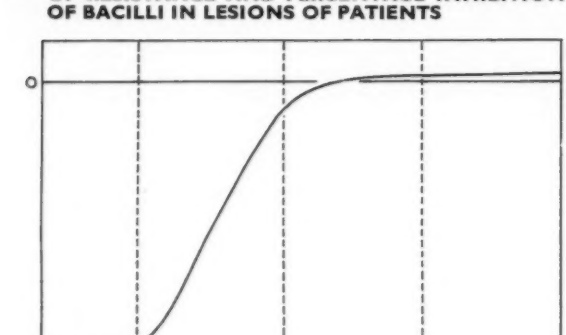
We now require to know whether resistant bacilli in the lesions of patients will grow during treatment with the drug when this is used alone. Figure 4 represents a hypothetical relationship between the response to treatment and the degree of resistance. At A the bacilli are sensitive and they stop growing. As resistance increases they begin to grow slowly (B). At C they are sufficiently resistant to grow at, say, 90% of their normal rate (i.e., almost completely free growth). The degrees of resistance indicated by B and C depend, of course, on the concentration of the drug to which

[1] See also Smith & Vollum, p. 140 of this number of the Bulletin.—ED.

TABLE I. THE INCIDENCE OF DRUG-RESISTANT CULTURES OF TUBERCLE BACILLI AFTER THREE MONTHS' TREATMENT OF PATIENTS WITH ACUTE PULMONARY TUBERCULOSIS

Drug	Total number of patients with positive cultures tested	Patients with resistant cultures	
		Number	Percentage of total
Streptomycin . . .	40	28	70
p-Aminosalicylic acid (PAS)	37	9	24
Isoniazid . . .	45	31	69

FIG. 4. HYPOTHETICAL RELATION BETWEEN DEGREE OF RESISTANCE AND PERCENTAGE INHIBITION OF BACILLI IN LESIONS OF PATIENTS



Vertical scale: percentage inhibition of bacillary growth in vivo
Horizontal scale: increasing resistance ratio

At A, bacilli are sensitive and stop growing
At B, resistant strains begin to be able to grow
At C (release resistance ratio), growth is at almost normal rate
At D, strains resistant to isoniazid to a degree greater than this have low virulence

The curve is drawn to rise slightly above the 0% value for inhibition. This indicates that the pathogenicity of resistant strains may sometimes be slightly increased by treatment (Steenken & Wolinsky, 1948; Barnett, Bushby & Mitchison, 1953b; Mitchison, 1954).

the bacilli are exposed, and hence upon the dosage used in treatment. The degree of resistance indicated by C, for the concentrations attained in patients by treatment with 1 g. of streptomycin/day or 200 mg. of isoniazid/day, will be called the "release resistance ratio". Methods of determining PAS resistance are so imprecise that it is impracticable to estimate a similar ratio for PAS.

a. Methods

Given below are the methods used for assessing the general clinical significance of resistance. If they are sufficiently accurate they may be used to obtain approximate values of the release resistance ratio.

i. *Clinical response.* During treatment with one drug the progress of those with resistant tubercle bacilli may be compared with those in which they remain sensitive. Since the patients who are most ill are also those who tend to yield resistant strains earliest and to the highest degree, the two groups must be compared, with adjustments made to equalize the initial severity of their disease. Even when this has been done the method is inaccurate and may lead to biased conclusions. Nevertheless it gives us valuable but not conclusive evidence as to the clinical significance of resistance, but little evidence as to the level of the release resistance ratio.

ii. *Increase of resistant bacilli in sputum.* During treatment there is first a fall in the number of sensitive bacilli in the lesions (measured by counts of stained bacilli in films of the sputum or preferably by viable counts). There is then a slow rise in the counts when the bacilli become resistant (as occurs in vitro; see fig. 1), which indicates that they can grow in the lesions. While bacilli in the sputum are resistant at the release ratio the rate of the rise will be the same as when the bacilli are more resistant, since all the bacilli can grow freely in treated lesions. However, if the bacilli are less resistant than the release ratio, the rate of rise will be slower. Thus the lowest degree of resistance emerging during the period of increasing bacillary counts is the release resistance ratio, so long as the rate of increase is the same as when strains with higher degrees of resistance emerge.

iii. *Selective pressure on heterogeneous resistant populations.* Evidence will be presented later that there may be bacilli of widely different degrees of resistance within the lesions of a patient. Bacilli with a lower degree of resistance than the release ratio will tend to be eliminated, whereas there will be little selective pressure against those with a higher degree of resistance. For instance, there may be marked fluctuations in the degree of resistance of bacilli in successive cultures from patients during prolonged treatment with streptomycin, probably reflecting a very heterogeneous population of bacilli in the lungs. The lowest level of resistance to which these fluctuating cultures fall is an estimate of the release resistance ratio.

iv. *Inverse resistance during combined therapy.* If a patient had a pre-treatment strain resistant to drug A and is then treated with drugs A and B, he may develop resistance to drug B at the same rate as if drug B were being given alone. This is evidence that drug A had no inhibitory effect on the mutants in the strain originally resistant to drug B and, therefore, if no cross-resistance exists between A and B, no inhibitory effect on the whole of the original strain. Under these circumstances the rate of emergence of resistance to drug B could be used to estimate the release resistance ratio to drug A, but so far this has not been done.

v. *Serum drug concentrations.* Tentative conclusions as to the significance of different levels of resistance have been drawn from studies of the blood concentrations of the various drugs found during the treatment of human patients. The medium used for determining the minimal inhibitory concentration for strains in vitro should resemble in composition the milieu within the lesion. It is unlikely that peak tissue concentrations would be higher than peak serum concentrations, so that an upper limit to estimates for the release resistance ratio can be obtained. This estimate can be no more than an upper limit, since a large number of assumptions must be made as to the ability of the drug to penetrate to the site of growth of the tubercle bacilli and as to its activity after penetration. During continuous treatment, drug concentrations in inflammatory exudates fluctuate less than do those in the blood, so that peak concentrations in the neighbourhood of the bacilli will be less than those in the blood. It has been assumed in many cases that there will be poor penetration of drugs to bacilli growing at the edge of fibrous-walled cavities. There seems little evidence in favour of this view, since the blood supply of cavities and other tuberculous lesions through the bronchial arteries appears to be remarkably good (Cudkowicz, 1952).

vi. *Response to treatment of tuberculosis of experimental animals.* Important conclusions can be drawn from the use of experimental tuberculosis in animals. Resistant strains have been injected into a variety of animals by a variety of routes (Feldman, 1951). The responses to treatment with

specific drugs have been noted. The following methods are of interest.

The intracorneal route of infection in mice and rabbits (Gardiner, Rees & Robson, 1949; Rees & Robson, 1950) provides a lesion that can be observed directly so that the effect of therapy is seen very rapidly. This method provided the earliest evidence that isoniazid-resistant strains did not respond to treatment with isoniazid (Goulding, King, Knox & Robson, 1952; Goulding & Robson, 1952). However, the test in mice gave no indication that the laboratory strain H37Rv and its isoniazid-resistant variant differed in virulence, whereas it was later shown (Mitchison, 1954) that the resistant variant used was, in fact, of low virulence. One can conclude that the intracorneal test provides a rapid, but rather crude, test of the significance of resistance.

The more conventional mouse test in which the infection is given by the intravenous route has been widely used to study the response of resistant strains to treatment. Probably a much higher proportion of tubercle bacilli grow intracellularly in the lungs of mice than in the lungs of man. Isoniazid penetrates well into cells, streptomycin penetrates poorly and PAS does not penetrate at all (Mackaness, 1952). Accurate assessments of the release resistance ratio of PAS and streptomycin that would be of clinical significance in man could, therefore, hardly be expected from this type of test.

The guinea-pig test appears to be the most satisfactory, although the disease simulates miliary rather than chronic fibroid tuberculosis in man. A high degree of allergy develops, as in man, so that the bacilli grow mainly in extracellular sites during the allergic phase of the disease and can then be killed by streptomycin (Jensen, 1949). The blood levels of the drug in the treated guinea-pigs should be about the same as those found in treated human patients if one is to draw conclusions as to the significance of given levels of resistance.

b. Significance of Streptomycin Resistance

Patients who developed streptomycin-resistant strains have been shown to make less clinical progress during continuing streptomycin therapy than those whose strains remained sensitive, irrespective of the initial degree of illness of the patients (Medical Research Council, 1950; see also Table III in Mitchell, Meade & Steenken, 1953). Furthermore, when patients with streptomycin-resistant strains were treated with streptomycin plus isoniazid they developed strains resistant to isoniazid at the same rate as if they were receiving isoniazid alone (see Table II). Both of these findings indicate that streptomycin-resistant strains do not respond to treatment with streptomycin in human pulmonary lesions, but they fail to provide an estimate of the release resistance ratio.

In the consideration of possible values for the release resistance ratio, only data from patients who received 1 g. of streptomycin/day will be used. Peak serum concentrations are 20–40 units/ml., and sensitive bacilli are inhibited in medium without Tween by about 1 unit/ml.[a] The release resistance ratio is, therefore, not likely to be more than 40.

During treatment a third to a half of patients may yield cultures with a resistance ratio which persists at about 4 (Medical Research Council, 1950; Bignall *et al.* 1950). In these patients there is a fall in the number of bacilli in the sputum while the strains remain sensitive, and a rise when they become resistant. This rise occurs at the same rate as in patients who develop more highly resistant strains (Mitchison, 1950). Furthermore, when strains fluctuate in the degree of resistance, the cultures with the lowest degree of resistance have a resistance ratio of about 4 (see fig. 2 in Mitchison, 1949, and Table V in Mitchison, 1950). Steenken & Wolinsky (1948) observed the response of guinea-pigs infected with a series of strains with low degrees of resistance to treatment with a dose corresponding to about 1 g./day in man. Considering only those strains inhibited by 10 units/ml. in Tween-albumin medium, they failed to find a good correlation between the sensitivity of the strains and their response. However, their sensitivity tests would detect as few as 0.1% resistant bacilli. An estimate of the proportion of resistant bacilli in the strains can be obtained from their data on cultures from the untreated animals, which were derived from tests both on solid and in liquid media. If this is done, the presence of bacilli capable of growth on the American Trudeau Society egg medium slopes containing 3.5 units/ml. (which just inhibits sensitive strains), but not on those containing 15 units/ml., appears to have been the factor deciding that there would be an absence of response. Such bacilli, which were presumably capable of growth in the treated animals, would have a resistance ratio of 2–8. All the available evidence thus suggests that the release resistance ratio for streptomycin is about 4.

TABLE II. THE INCIDENCE OF RESISTANCE TO ISONIAZID AFTER THREE MONTHS' TREATMENT WITH ISONIAZID, AND WITH ISONIAZID PLUS STREPTOMYCIN, SHOWN ACCORDING TO INITIAL STREPTOMYCIN SENSITIVITY (Medical Research Council, 1953a)

(SH denotes treatment with streptomycin plus isoniazid; H denotes treatment with isoniazid alone)

Initial streptomycin sensitivity	Treatment	Total number of patients with sputum cultured	Number of patients with positive cultures tested	Patients with cultures resistant to isoniazid	
				Number	Percentage of total
Sensitive	H	93	53	33	35
Resistant	H	4	2	1	25
Sensitive	SH	109	23	3	3
Resistant	SH	7	4	4	57

c. Significance of p-*Aminosalicylic Acid* (*PAS*) *Resistance*

Comparatively little is known about the significance of PAS resistance. In none of the major clinical trials where PAS was used alone was the effect of PAS resistance or the subsequent response of the patient analysed. There is evidence that those patients who have strains initially resistant to PAS and are subsequently treated with streptomycin plus PAS develop strains resistant to streptomycin much more rapidly than do those with strains initially sensitive to PAS (see Table III and Turnbull, Wallace, Stewart & Crofton, 1953). Furthermore, infections due to PAS-resistant cultures in animals have failed to respond to treatment with PAS (Swedberg, 1949; Karlson, Delaude & Feldman, 1949; Karlson & Feldman, 1952). Thus the evidence suggests that strains resistant to PAS in vitro are also clinically resistant. The degree of resistance is of little significance since strains resistant to PAS, unlike those

[a] The unit of streptomycin is defined in such a way that it is equivalent to the activity contained in 1 μg. of pure streptomycin base.

resistant to streptomycin and to isoniazid, show no sharp end-point concentration of PAS above which their growth is suddenly inhibited. The determination of the end-point concentration is thus very inaccurate.

d. Significance of Isoniazid Resistance

In the MRC trials (Medical Research Council, 1952b) patients who were known to have resistant strains benefited less from continued treatment with isoniazid than did those who were not known to have resistant strains. This was found to be true irrespective of the initial illness of these patients. In addition, a fall in the number of bacilli in the sputum followed by a rise when the strains became resistant has been demonstrated during treatment of patients with isoniazid and was found to be associated with clinical relapse (Joiner, MacLean, Pritchard, Anderson, Collard, King & Knox, 1952; Coates, Meade, Steenken, Wolinsky & Brinkman, 1953).

Peak serum levels of isoniazid in patients in the MRC trials have been found to average 1–2 μg./ml. (Cuthbertson, Ireland, Woolf & Kuper, 1954). Guinea-pigs treated with the same dosage and having similar serum concentrations were infected with strains of varying degrees of resistance (Mitchison, 1954). Strains growing on Löwenstein slopes containing 1 μg./ml. but yielding little or no growth on 5 μg./ml. failed completely to respond to treatment, whereas a strain growing on 0.2 μg./ml., but not on 1 μg./ml., was only partially prevented from growing. This suggests that a strain with the release resistance ratio would be just inhibited on slopes containing an isoniazid concentration somewhere between 1 μg./ml. and 5 μg./ml. It is likely that this concentration would be nearer 1 μg./ml. than 5 μg./ml., since guinea-pig tuberculosis caused by another strain growing on 1 μg./ml., but not on 5 μg./ml., was also not affected by treatment at a dose level five times higher (Barnett, Bushby & Mitchison, 1953b). Since sensitive strains are inhibited by about 0.1 μg./ml. on Löwenstein medium, a rough estimate of the release resistance ratio is thus 10.

5. Homogeneity of Resistant Strains

Streptomycin-resistant mutants with low degrees of resistance (resistance ratios of about 4) occur 10 to 100 times more frequently in any sensitive strain than do more resistant mutants (Mitchison, 1951). Since we have evidence that the release resistance ratio is about 4, why do not all resistant strains eventually consist almost entirely of bacilli with low degrees of resistance? In some patients this occurs. In others strains of greater resistance appear. It is suggested that even at the release resistance ratio there is still some slight selective pressure favouring the growth of mutants with higher degrees of resistance. These are of two varieties, one with resistance ratios of about 100 and the other with resistance ratios of more than 1,000 (Mitchison, 1949, 1951). These two types occur with about the same frequency in sensitive populations (Mitchison, 1953a, 1953b). As they grow, they may be prevented from spreading throughout the lesions by the defence mechanism of some patients and by the type of their lesions. In such cases successive cultures continue to have a resistance ratio of about 4. In other patients they not only grow but also spread through the lesions and gradually or rapidly replace bacilli with a low degree of resistance. It may be of significance that Crofton & Mitchison (1948) and Bignall *et al.* (1950) found correlations between clinical progress before the development of resistance and the ultimate degree of resistance and also between confluence of radiological shadows before treatment and the degree of resistance.

One would expect that once strains had become fairly uniformly composed of bacilli resistant at the release resistance ratio level they would continue to be homogeneous at that level. However, there would be widespread variations both in the degree of resistance and in the uniformity of strains at higher levels of resistance. This was found to be true not only of strains in the sputum (Mitchison, 1950), but also of strains isolated from different cavities in the same lungs (Medlar, Bernstein & Reeves, 1951).

The interval between a strain first appearing resistant in a sensitivity test and when it is fairly uniformly resistant at the release resistance ratio is usually less than six weeks (Mitchison, 1950). Therefore, in patients treated with streptomycin alone, a report that a strain was resistant usually implies that treatment should be discontinued at the time of the receipt of the report (i.e., six weeks after the sputum was cultured).

After treatment, non-cavitating lesions tend to contain strains with a lower degree of resistance (Medlar *et al.* 1951; Canetti & Saenz, 1951). Such sites may have pre-treatment populations of bacilli too small to contain resistant mutants, or the defence mechanisms may be more efficient than in cavities. Furthermore, they sometimes appear to contain a proportion of sensitive bacilli even after strains in the sputum have become resistant. These sensitive bacilli are probably "persisters" (Bigger, 1949) which have failed to grow and have therefore not been killed by the streptomycin (Middlebrook & Yegian, 1946; Garrod, 1948). They are present in such small numbers that continued treatment with streptomycin would be unlikely to benefit the patient.

There is little evidence as to the distribution of isoniazid-resistant bacilli throughout the lungs. In the author's experience multiple cultures from different lesions in the lungs of two patients with isoniazid-resistant strains in the sputum were all resistant.

These conclusions probably do not apply to some resistant strains which arise during treatment with a combination of drugs of patients whose pre-treatment strains were sensitive to both drugs.

6. Treatment with Two Drugs Combined

The simultaneous use of two drugs has been shown to be effective in preventing drug resistance to both of the two drugs used (Medical Research Council, 1950, 1952a, 1953c, 1953d)[3], so long as pre-treatment cultures were sensitive to both drugs. Only about 1–4% of patients developed resistant cultures after treatment for three months.

During combined therapy some patients continue to have sensitive strains in their sputum for several months. How do these organisms arise? There might be some lesions in the lungs in which sensitive bacilli continue to divide because the drug does not penetrate to them. A second possibility is that any bacilli that divide are killed by the drugs; that there is virtually no division of sensitive bacilli once chemotherapy has started and that all the bacilli that occur in the sputum

[3] See also papers by Fox (p. 108) and Scadding (p. 135) in this number of the Bulletin.—Ed.

are part of the original population present in the lesions at the beginning of therapy. One must remember that tubercle bacilli can lie dormant for very long periods. Thus Corper & Cohn (1951) sealed up cultures growing on the surface of liquid media. After 30 years of storage at 37° C. these were opened and 1% of many of the original culture populations was still viable.

Lines of evidence in favour of the second possibility are as follows :

i. If sensitive bacilli continued to divide, one would have to presume gradients of drug activity within some of the lesions so that in parts of them there would be bacilli growing and in other parts bacteriostasis. Now the three drugs differ markedly in properties that might be expected to affect their activity in lesions, such as diffusion rates, ability to penetrate cells, effect of changes in pH and inhibition by *p*-aminobenzoic acid. One would, therefore, expect different gradients of activity for each drug and, during treatment with a combination of drugs, there would be regions in which only one drug was present in sufficient quantities to stimulate the development of resistance. Such regions would be foci for the rapid development of drug resistance. However, all three of the double combinations are efficient in preventing the emergence of resistance, so that this hypothesis seems unlikely.

ii. It is well recognized that miliary and acute exudative tuberculosis respond much more quickly to chemotherapy than does chronic disease with caseation or cavitation, especially when the response is measured by the sputum conversion rate. Furthermore, experimental tuberculosis in guinea-pigs and mice, which corresponds to highly acute miliary disease in man, responds even more rapidly. If one assumes that sensitive bacilli continue to grow during treatment, the most reasonable explanation of these findings is that the drugs fail to penetrate certain types of human lesions found most commonly in chronic disease, presumably cavities. However, streptomycin has been found in cavities in amounts well above those necessary for bacteriostasis (Steenken, D'Esopo & Wolinsky, 1947). Furthermore, streptomycin-resistant bacilli occur more uniformly and to a higher degree of resistance in cavities than in other lesions.

An easier explanation can be provided if one assumes that sensitive bacilli do not continue to divide during treatment. In this case the effectiveness of the drugs used will depend upon their bactericidal activities. Now in vitro the speed at which a culture is sterilized by any given concentration of streptomycin or isoniazid is determined in part by the speed at which the organisms are growing in the culture (Middlebrook & Yegian, 1946; Mackaness & Smith, 1953) and in part by the total number of them that are to be killed. The rate of killing of bacilli would be slowest in chronic disease, where there is a large bacterial population at least part of which is growing slowly. Killing would be most rapid when there is a small population growing with uniform rapidity, as in miliary tuberculosis.

iii. If sensitive bacilli continued to divide during therapy, drug resistance would tend to develop by multiple-step selection in the drug gradients present in the lesions. If no division occurred, resistance would develop by single-step selection. As has been pointed out in section 1, streptomycin resistance probably originates by single-step rather than by multiple-step selection.

All these arguments suggest that, in fact, 1 g. of streptomycin/day and 200 mg. of isoniazid/day (the dosages employed in the MRC trials) flood all the lesions in active concentrations and are thereafter adequate to prevent the growth of sensitive organisms.

If this hypothesis be true, the relative speeds at which different schemes of combined therapy kill tubercle bacilli in lesions depend solely upon the bactericidal activity of the drugs at the sites of the bacilli. This assumes that the development of drug resistance has been virtually abolished, and that none of the drugs influences the defence mechanism of the patient. One of the major difficulties in designing in-vitro tests of the bactericidal activity of drugs is to know the peak level of drug activity within the lesions. This can be estimated from a knowledge of the release resistance ratio. The release resistance ratio for streptomycin is about 4 and for isoniazid is about 10, so that the equivalent of the peak tissue concentration in any artificial medium would be the minimal inhibitory concentration of the sensitive strain H37Rv in that medium multiplied by the release resistance ratio. For instance, if in Dubos medium the minimal inhibitory concentrations of H37Rv are 0.5 units/ml. streptomycin and 0.05 μg./ml. isoniazid (Mitchison, 1952), then the equivalents of the peak tissue levels would be 2 units/ml. streptomycin and 0.5 μg./ml. isoniazid. We can thus develop rational in-vitro methods, similar to those illustrated in fig. 1, for assessing the relative rates at which different combinations of drugs will kill tubercle bacilli in patients.

7. Drug Resistance during Combined Therapy

By far the most important reason for the development of resistance in patients receiving therapy is that the strain obtained before treatment was started is already resistant to one of the drugs in the combination. This will usually have arisen as a result of previous treatment with this one drug alone. In these patients resistance to the second drug in the combination then develops as if it were being given alone (Medical Research Council, 1953a, 1953c). This is illustrated in Tables II and III. Two conclusions can be drawn from these findings: (i) no chemotherapeutic drug should ever be used by itself; (ii) delicate and reliable tests to detect drug resistance must always be carried out on pre-treatment cultures. They should be sufficiently delicate to detect degrees of resistance from B in fig. 4 upwards, since even strains that are only partially inhibited in the lesions by one drug could contain mutants resistant to the second drug, and doubly resistant bacilli could slowly grow. This explains

TABLE III. THE INCIDENCE OF RESISTANCE TO STREPTOMYCIN AFTER THREE MONTHS' TREATMENT WITH STREPTOMYCIN PLUS *p*-AMINOSALICYLIC ACID (PAS), SHOWN ACCORDING TO INITIAL PAS SENSITIVITY (Medical Research Council, 1953c)

Initial PAS sensitivity	Previous therapy with PAS alone	Total number of patients with sputum cultured	Number of patients with positive cultures tested	Patients with cultures resistant to streptomycin	
				Number	Percentage of total
Sensitive	No	219	68	4	2
Sensitive	Yes	11	4	1	9
Resistant	Yes	10	8	7	70

why such emphasis was laid earlier in this article on detecting even low degrees of resistance. Testing of at least two pre-treatment cultures is advisable. Failure to carry out pre-treatment sensitivity tests or to carry them out by techniques which fail to detect these low degrees of resistance appears to be a major reason why trials in the United States of America have found a high incidence of drug resistance during combined therapy and have failed to distinguish clearly the effects of pre-treatment resistance. (See discussions in Mitchell, 1952, and in Medical Research Council, 1953c.)

However, in spite of the use of delicate techniques to detect pre-treatment resistance, a very small percentage (1–4%) of patients with initially sensitive strains still yield resistant strains during combined therapy. Why does this occur ? The mechanisms suggested have, as yet, rather little experimental backing.

i. Some pre-treatment cultures may contain an abnormally high proportion of resistant bacilli which are not detected. This seems unlikely to account for all cases since almost all the patients who developed resistant strains during combined therapy in the MRC trials had received no previous chemotherapy. Not more than 1% of these patients had detectably resistant cultures and they were excluded from the analysis. One would have to assume that another 1–4% of them had resistant cultures which could not be detected.

ii. Reasonable estimates for the proportion of mutants of low resistance in sensitive cultures growing in Tween-albumin medium are about 1 in 10^6 for streptomycin (Mitchison, 1951) and 1 in 10^5 for isoniazid (Mitchison, 1953b). Since clumping occurs in this medium the real proportions are likely to be more nearly 1 in 10^7 and 1 in 10^6 respectively. Double mutants, resistant to streptomycin and isoniazid simultaneously, would then occur once among 10^{13} sensitive bacilli, a total population that is unlikely to occur in the lesions of a single patient even if he had severe disease.

iii. Let us assume that two actively bactericidal drugs such as streptomycin and isoniazid are acting continuously on an initially sensitive population as illustrated in fig. 1. The bactericidal action of the combination is greater than that of streptomycin or isoniazid alone (Mackaness & Smith, 1953; Hobby, Lenert, Rivoire, Donikian & Pikula, 1953; Singh & Mitchison, 1954). Mutants resistant to either drug will be killed less rapidly than sensitive bacilli because only a single drug acts on them. Although their absolute numbers are still decreasing, their proportion within the residual viable population will tend to increase. Thus the strain will appear to become more and more resistant to both drugs.

Within such resistant strains the population of bacilli resistant to streptomycin will be separate from the population resistant to isoniazid since these bacilli are the remnants of the original mutant populations which were independent of each other. Therefore the bacilli resistant to either drug will be killed by the other. In consequence the culture in vitro, and presumably in vivo also, would be completely sterilized by the combination in spite of appearing resistant to both. Furthermore, although strains would appear resistant to each drug separately in vitro, they would appear sensitive in an in-vitro test with both present simultaneously in the same medium (Rothstein, 1952). Since the population of residual mutants would be small, individual mutant bacilli resistant to only one drug could be sampled in some cases and the strain would then appear resistant to this one drug only. We can conclude that strains apparently resistant by this mechanism may still be acted on by combined treatment in the lesions of patients.

iv. The circumstance that would limit the effectiveness of combined therapy would be simultaneous resistance of the same bacterial population. It could be measured by resistance tests carried out against both drugs in the same medium. This type of resistance would be expected to develop (apart from mechanisms (i) and (ii) above) if either one or both of the drugs were administered in a sufficiently intermittent manner or in a sufficiently low dosage to allow growth either of resistant mutants or of the whole strain. In such cases the population resistant to one drug might become sufficiently numerous to contain mutants resistant to the other drug, which would then be able to grow freely. Thus this mechanism involves the appearance of resistance first to one drug and then to the other.

As an example, streptomycin has sometimes been given in an injection of 1 g. twice a week together with isoniazid 100 mg. twice a day (S2H treatment). Here one would expect mutants resistant to isoniazid to grow to some extent during the interval that streptomycin was not being given. Thus they would form an increasing proportion of the strain, which would then appear resistant to isoniazid only. If this isoniazid-resistant population were to become sufficiently large to contain mutants resistant to streptomycin, then doubly resistant bacilli would be present. These could now grow freely and would limit the effectiveness of the treatment.

In the MRC trials (Medical Research Council, 1953d) the proportion of cultures resistant or doubtfully resistant to isoniazid isolated from patients receiving the S2H treatment (13% of 94 patients) was greater than the proportion isolated from patients receiving isoniazid plus daily injections of 1 g. of streptomycin (SH treatment; 3% of 74 patients). There were, at most, slightly more streptomycin-resistant cultures obtained from patients getting S2H treatment (3% of 94 patients) than from those getting SH treatment (0% of 74 patients).

In the case of combinations involving PAS the mechanism involved would depend on the dosage employed. In high dosage PAS is bactericidal and mechanism (iii) would operate. In low dosage PAS allows some multiplication of bacilli so that mechanism (iv) would operate and result in the increased incidence of resistance that is found in practice (Medical Research Council, 1952a). Thus, in fig. 2, PAS at a low concentration only slows the growth of even small inocula of sensitive bacilli. It would also, no doubt, only slow the growth of mutants resistant to streptomycin, producing a strain resistant first to streptomycin and then to PAS.

In conclusion, the hypothesis presented is that the adequacy of combined chemotherapy depends upon the effectiveness with which sensitive bacilli are prevented from continuing to multiply and the speed at which they are killed. If we assume reasonable adequacy of treatment and pre-treatment cultures that are truly sensitive to both drugs, the only form of drug resistance that should appear will be transitory in nature. Resistant cultures may appear in tests on media containing the two drugs separately, but the bacilli will appear sensitive in tests on media containing the two drugs together; the appearance of such " resistant " cultures will shortly precede the disappearance of bacilli from the patient's sputum. A true relapse accompanied by resistance to both drugs tested in the same medium would suggest pre-treatment resistance to one of the drugs or inadequate treatment.

8. Virulence of Resistant Strains

There is an association between the virulence of tubercle bacilli to experimental animals and the degree of their resistance to isoniazid (Barnett, Bushby & Mitchison, 1953a, 1953b ; Middlebrook & Cohn, 1953; Mitchison, 1954). This was shown most clearly in guinea-pigs and is summarized in Table IV. The loss of virulence was not complete ; even the least virulent strains were more virulent than *Bacille Calmette Guérin* (BCG). The amount of disease produced depended upon the number of bacilli used for infection, but even small numbers of bacilli produced histological lesions that took two to three months to heal.

Strains of low or intermediate virulence in guinea-pigs were also of lowered virulence in mice and it has been reported that they also lack virulence in rabbits. One would, therefore, expect them to be of low virulence in human patients. Why then does clinical relapse occur in patients with resistant strains? Possible reasons are as follows :

i. The loss of virulence even when most marked is not complete.

ii. Strains capable of growth on 1 μg./ml. but not on 5 μg./ml. were often fully virulent and produced extensive disease both in untreated animals and in those treated with isoniazid in the same or greater dosage than is used in man. Thus the degree of resistance that ensures loss of virulence (D in fig. 4) is higher than the release resistance ratio (C in fig. 4). It is probably at 5–10 μg./ml. in Löwenstein medium (resistance ratio of 50 to 100).

iii. Treatment with isoniazid may increase the virulence of some resistant strains.

TABLE IV. THE RELATION OF VIRULENCE TO ISONIAZID RESISTANCE AMONG STRAINS OF TUBERCLE BACILLI (Mitchison, 1954)

Degree of isoniazid resistance*	Growth on 0.2 μg./ml. but not on 1 μg./ml.	Growth on 1 μg./ml. but not on 5 μg./ml.	Growth on 10 μg./ml. but not on 50 μg./ml.	Growth on 50 μg./ml.
Isoniazid concentration during subculture (μg./ml.)	0 or 0.2	0.2	1 or 10	50
Virulence in guinea-pigs				
full	3	2	0	0
intermediate	0	1	1	0
low	0	1	2	7†

* Measured on Löwenstein-Jensen slopes by the MRC method (Medical Research Council, 1953b).

† Three of these strains were variants of H37Rv, one having been obtained from a guinea-pig infected with H37Rv and treated with isoniazid.

The resistant strains described so far were composed of bacilli with fairly uniform degrees of resistance, since between isolation from patients and injection into the animals they were sub-cultivated on medium containing isoniazid in a slightly lower concentration than that necessary to inhibit the strain (see Table IV). When this procedure was not carried out (Peizer, Widelock & Klein, 1953; Steenken & Wolinsky, 1953 ; Bloch, Widelock & Peizer, 1953), a much less definite relation between degree of resistance and virulence was obtained and a considerable number of highly resistant strains were virulent. This is presumably because these strains contained a proportion of bacilli with a lower degree of resistance and higher virulence. We can thus conclude that a proportion of many isoniazid-resistant strains are of low virulence but that a complete absence of virulent bacilli is rare.

There is no convincing evidence that resistance to streptomycin or PAS results in any loss of virulence.

9. Conclusions

The following conclusions can be drawn about the choice of drugs and courses of treatment :

i. No chemotherapeutic drug should ever be given alone, since the development of resistance limits its action and prevents its successful use in later combined therapy.

ii. If a pre-treatment culture is resistant to a drug, then the use of that drug is contra-indicated in a double combination.

iii. Intermittent treatment with either or both drugs in a combination should be avoided, particularly at the beginning of treatment. PAS should be given in sufficiently large doses to ensure high peak serum levels.

If these principles are adhered to, the use and significance of sensitivity tests can also be summarized as follows :

1. The most careful determination of the sensitivity of pre-treatment cultures is essential, particularly if there is a history of previous chemotherapy. Even a slight degree of resistance to one drug implies that the other in the combination will be acting to some extent as if given alone. Improvements in technique should therefore be aimed primarily at increasing the reliability and delicacy of the test.

2. Further tests should seldom be necessary if the pre-treatment cultures were fully sensitive to both drugs and if treatment was continuous and in adequate dosage. A finding of resistance under these circumstances is of doubtful clinical significance, but may be of importance if a relapse occurs.

3. If a drug has been given alone or in such circumstances that it acts as if given alone (see (1) above), a report that the strain is resistant usually indicates that further treatment with the drug is of little value.

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SOME PROBLEMS IN PRIMARY TUBERCULOSIS

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1. Sources of Infection

There are only two significant sources of infection with tubercle bacilli: open cases of pulmonary tuberculosis, and milk.

a. Infection from Milk

The source of infection has an influence on the site of the primary lesion and the later fate of the patient. When the infection is derived from milk it will often affect younger children in whom the disease is more likely to become disseminated. The dissemination may take either the acute form of miliary tuberculosis or tuberculous meningitis, or a more chronic form such as bone tuberculosis, joint tuberculosis or genito-urinary tuberculosis.

The British Isles, and in particular Scotland, have acquired an unenviable reputation in the world's literature for bovine tuberculosis. This is mainly based on the painstaking work of the Royal Commission on the subject set up before the 1914–18 war. Some of these early figures continue to be quoted in textbooks. In fact over the last 20 years much has been done to eliminate the danger from milk, and we are well within sight of having entirely safe milk in Great Britain. In 1939, 4.95% of cattle in England and Wales were "attested" as tuberculosis-free; in 1952 this figure was 36.1% and it is now probably over 40%. In 1939, 4.9% of milk came from attested herds, in 1953, 55.5%. At present 86% of the milk produced in England and Wales is pasteurized or sterilized and probably less than 10% is neither pasteurized nor comes from tuberculin-tested herds. By 1952, 58.1% of Scottish cattle were "attested" and in 1952–53 97.9% of marketed milk was from attested herds. About 76% was pasteurized and fully 99% was either pasteurized or from attested herds.

In Great Britain the last considerable survey of bovine tuberculosis in man, as shown by actual typing of the bacilli from lesions, was made as a group effort about 10 years ago (Wilson, Blacklock & Reilly, 1952). Approximate figures are given in Table I. It seems likely that these proportions would be much smaller at the present time.

TABLE I. PROPORTION OF CASES CAUSED BY BOVINE BACILLUS

Site of disease	Period (years)	England (%)	Scotland (%)
Abdominal	Up to 1937–38	82	81
	1943–45	65	65
Meningitis	Up to 1937–38	25	26
	1943–45	28	11
Cervical glands	Up to 1937–38	50	78
	1943–45	57	68
Bone and joint	Up to 1937–38	20	38
	1943–45	11	11
Genito-urinary	Up to 1937–38	17	25
	1943–45	20	26

The 1943–45 figures are derived from the group survey (Wilson, Blacklock & Reilly, 1952); those for previous years are from various sources.

As indicated in Table I, a high proportion of tuberculosis in the intestines and peritoneum is likely to be due to the bovine bacillus, so that figures for deaths from this form of tuberculosis probably give some indication of the incidence of bovine tuberculosis in the community. Deaths from abdominal tuberculosis were 70 per 100,000 in 1911 but had fallen to 1.2 per 100,000 in 1948, before the influence of chemotherapy would have been significantly felt. Again, the death-rate from tuberculosis in young children will probably reflect to some extent the incidence of bovine infection. The effect of the pasteurization of milk in London is well shown by a comparison of the deaths from tuberculosis per 1,000,000 children under five years between 1921 and 1944 as shown in Table II. But from the figures for tuberculin positivity in children aged five years, as found in the Medical Research Council (MRC) National Tuberculin Survey in 1949–50 (Medical Research Council, 1952), it appears that infection from milk is probably still occurring to a notable extent in rural areas; the tuberculin test was positive in 9.3% of children at the age of five years in urban centres in the south of England, compared to 20.3% in areas in rural England and Wales. We can summarize by saying that in these islands the problem of bovine tuberculosis is on its way to solution but is not yet entirely solved.

TABLE II. PROBABLE EFFECT OF PASTEURIZATION OF MILK IN LONDON (adapted from Clarke, 1952)

Locality	Deaths from tuberculosis/1,000,000 children under 5 years of age				Ratio of death-rate in 1944 to that in 1921
	1921		1944		
	Deaths/ 1,000,000	Total deaths	Deaths/ 1,000,000	Total deaths	
London	136	51	6	1	0.044
Combined rural districts	252	176	60	37	0.238

b. Infection from Man

If we agree that the main sources of infection at the present time are cases of pulmonary tuberculosis, it is clear that such sources must be very common in the community, or that the disease is highly infective, or both. The MRC National Tuberculin Survey already quoted showed that, by the age of 19–20, 59.3% of the individuals tested in southern urban districts of England, 73.6% in northern urban districts, and 65.0% in rural England and Wales were tuberculin-positive (Medical Research Council, 1952).

2. Site of Primary Tuberculous Lesions

The three main sites for the primary tuberculous lesion are the lungs, the intestines and the tonsils. With the decrease of infection from milk the great majority of primary lesions are now found in the lungs. But Miller (1953) has shown in 28 patients that primary infection may occur on the skin or mucosae. These lesions may be diagnosed by the presence of a local tuberculous lesion combined with the enlargement of the draining glands; this indicates that the lesion is a primary one. The local lesion has usually to be proved by biopsy. In primary infections of the tonsils and the intestines the lesion at the site of entry is negligible, the only clinical manifestation being the enlarged draining glands. In the case of the lung the size of the parenchymal lesion is very variable and often it is impossible to detect on the radiograph even when the pathological specimen is available for comparison with the film (Macgregor & Alexander, 1937).

3. Age and Primary Tuberculous Infection

The age at which the individual receives his first tuberculous infection has a considerable influence on its outcome. There is a good deal of evidence to show that, whereas previously the majority of the population received its first infection in childhood, nowadays an important proportion is first infected in adolescence or early adult life. In the MRC National Tuberculin Survey in 1949–50 (Medical Research Council, 1952), it was found that in urban areas the annual infection-rate, as shown by tuberculin positivity, was approximately twice as high between the ages of 15 and 20 as between 6 and 14, in the school years, although increase at ages 15–20 did not occur to the same extent in rural areas. The influence of age on the morbidity and mortality from tuberculous infection may be summarized in tabular form (Table III).

TABLE III. THE INFLUENCE OF AGE ON MORTALITY AND MORBIDITY AFTER PRIMARY TUBERCULOUS INFECTION (adapted from Clarke, 1952)

	Age (years)			
	Under 1	1–4	5–12	Adolescents and young adults
Immediate morbidity	High	High	Low	Low
Immediate mortality	High	Low	Low	Low
Late morbidity	Low	Low	Low (but includes skeletal disease)	High (mainly pulmonary disease)

The high morbidity and mortality in infants are mainly due to the development of miliary tuberculosis and tuberculous meningitis. Children of school age have a higher resistance to tuberculosis, but in this group the more chronic forms of dissemination, such as skeletal tuberculosis, are particularly likely to occur. In adolescents and young adults the immediate morbidity and mortality are low but it is in this age-group that the bulk of post-primary pulmonary tuberculosis occurs. The later age of primary infection at the present time, compared with previous years, may be one reason for the increased incidence of pulmonary tuberculosis in Scotland since the 1939–45 war. A few figures may be quoted in support of the statements in Table III. In Copenhagen (Holm, 1946) it was found that in children showing tuberculin conversion between the ages of one and six, radiographic abnormalities in the lung were found in 32.3% and tubercle bacilli were demonstrated in 13.2%, whereas, in adults showing tuberculin conversion, radiographic changes were found in 14% and tubercle bacilli were demonstrated in 6.2%. In Papworth Village Settlement for tuberculous patients at Papworth Everard, Cambridgeshire, among 108 children born in the village no clinical case of tuberculosis occurred, though in nearly 50% transient radiographic shadows or residual calcification were found (Brieger, 1944). In the Prophit Tuberculosis Survey (Daniels, Ridehalgh, Springett & Hall, 1948), radiographic changes were found in approximately 8% of young adults on tuberculin conversion and in nearly half of these there was later clinical evidence of post-primary pulmonary tuberculosis.

The manifestations of primary pulmonary tuberculosis also vary with age. The hilar glandular component is more obvious in the child though he is more capable than the adult of limiting the parenchymal lesion in the lung. In the child the parenchymal component of the primary complex may occur anywhere throughout the lung but in adolescents and adults the lesion is more commonly seen in the upper zones and the glandular component is often not detectable radiographically (Daniels *et al.* 1948). In mass miniature radiographic surveys in the Royal Navy, Brooks (1946) found that, with increasing age, the classical appearances of primary pulmonary tuberculosis, with parenchymal and glandular components, became less common, whereas the classical appearances of post-primary pulmonary tuberculosis became more so. It is clear that it may be impossible to differentiate between primary tuberculous infection and a post-primary tuberculous infection in adolescents or in young adults unless recent tuberculin conversion can be demonstrated.

4. Clinical Manifestations of Primary Tuberculosis

The incidence of clinical manifestations will probably depend on very many factors, the two main ones being the size of the infecting dose and the resistance of the individual to the disease. It is not surprising therefore that different observers have recorded very different figures for clinical manifestations found on tuberculin conversion. Transient fever is usually regarded as the most common feature, particularly in children. Some Scandinavian writers (Wallgren, 1935) consider that it is almost universal in children, others (Ustvedt, 1946) that it is very common. In the Prophit Tuberculosis Survey in young adults (Daniels *et al.* 1948) more than 70% of those showing tuberculin conversion

recorded no significant symptoms. As mentioned, the incidence of symptoms probably varies with the size of the infecting dose; Malmros & Hedvall (1938) found symptoms much commoner in student nurses and medical students than in others. Although the aetiology of erythema nodosum may differ widely, this is a not uncommon accompaniment of primary infection. Its predilection for females is well known. It is possible that there is some genetic factor in susceptibility to erythema nodosum, for this manifestation appears to be much commoner in Scandinavian countries than in Great Britain. Approximately 1.8% of 782 tuberculin conversions in young adults in the Prophit Tuberculosis Survey developed erythema nodosum. Thompson (1952) found an incidence of 1.3% in children under 14. These are lower than most Scandinavian figures, for example, 6% (Malmros & Hedvall, 1938), 15% (Heimbeck, 1937), 11% (Hyge, 1947) and 4.9% to 8.5% according to age (Meyer, 1949). The latter found the maximum incidence in the 4–12 year age-groups.

5. The Problem of Epituberculosis

The term "epituberculosis" was coined by Eliasberg & Neuland (1920, 1921). This is primarily a radiographic conception and their original description might be translated as: "A dense homogeneous shadow, extending, without any areas of translucency, over a complete lobe of the lung from the hilum to the periphery". This condition always occurred in children with positive tuberculin tests and it was noted that under treatment the general condition and weight soon improved but that the radiographic shadow persisted for months, after which it gradually became smaller and tended to clear, often leaving a residual shadow round the hilum, which was attributed to enlarged glands. This phenomenon has been very generally recognized since the original description but there is no uniformity of opinion as to the nature of the shadow. Owing to the good prognosis few autopsies or biopsies have been carried out. Although in the original cases the shadows were confined to the upper lung fields, it is now realized that they may occur in any part of the lung and may involve segments of lobes as well as complete lobes. It is also recognized that epituberculosis is almost always, if not always, associated with enlarged tuberculous lymph glands at the hilum. It seems probable that the radiographic appearances may be caused by any of three pathological phenomena: collapse, inflammatory exudation with minimal caseation, or caseous pneumonia. Each may occur either alone or in combination with one or more of the others. Collapse of an area of lung is associated with the glandular component of the complex. The collapse is produced either by pressure of the gland on the bronchus; or by the direct spread of tuberculous infection from the gland to the bronchus, which results in blockage of the lumen by granulation tissue; or by caseous material discharged through the damaged bronchial wall. Later the bronchial lesion may heal with a residual fibrous stenosis. Macgregor & Alexander (1937) consider that the collapse is more often due to the occlusion of the smaller bronchi by inflammatory exudate or caseous material from the primary parenchymal lesion. The second possible lesion responsible for epituberculosis is an exudate of inflammatory cells with minimal caseation. Only a biopsy can prove both that this is the underlying pathological condition and that the shadow will eventually clear. Post-mortem material is subject to the criticism that one of the criteria of epituberculosis is that the lesion resolves. Rubinstein (1928) carried out a formal biopsy on a child with consolidation of the middle lobe in the belief that it was an empyema. The histology showed consolidation, giant cells, epithelial cells, lymphocytes, fibroblasts and small areas of caseation. Subsequently the child made a complete recovery. Unfortunately no tuberculin test is recorded and the sections were apparently not stained for acid-fast bacilli; but Spence (1932) and Gorter & Lignac (1931) have recovered tubercle bacilli by lung puncture in other cases. Histological appearances similar to those of Rubinstein's case have been recorded in post-mortem examinations of children, including one of Eliasberg and Neuland's original cases, dying from meningeal tuberculosis or from other diseases (Eliasberg & Neuland, 1921; Armand-Delille & Lestocquoy, 1931; Cameron & De Navasquez, 1936; Macgregor & Alexander, 1937; Fish & Pagel, 1938). Reichle (1933) has recorded two fatal cases in which the main exudate was due to polymorphonuclear cells although numerous tubercle bacilli were present. Radiographic appearances, similar to epituberculosis and later disappearing, have occurred during a severe tuberculin reaction (Langer, 1923) and after experimental introduction of killed bovine bacilli intratracheally into hypersensitive rabbits; histologically the lesions in the rabbits consisted of tuberculous pneumonia, including caseation (Oppenheimer, 1935). Caseous pneumonia has of course been recorded in numerous autopsy studies and its existence can often be implied by subsequent calcification shown by the radiograph. Whether caseous material might reabsorb, leaving normal lungs, may be regarded as uncertain, though in Oppenheimer's rabbits only slight residual scarring remained when the radiographic shadow had cleared. If the lung tissue itself is involved in the caseous process, in contradistinction to caseation of the inflammatory exudate, it seems hardly possible that the lung could ever be restored to its previous state. Adler & Richards (1953), in describing 86 cases of consolidation or collapse consolidation in children, stated that no instance of caseous pneumonia had occurred in a large hospital for childhood tuberculosis during the period of three years that they were reviewing. It is suggested that in a number of cases a comparatively benign exudative lesion may be caused by the aspiration into a segment or lobe of caseous material derived from a gland eroding into a bronchus. This material may contain a few tubercle bacilli and perhaps a great deal of tuberculoprotein which may give rise, after an initial collapse of the area concerned, to considerable exudation of inflammatory cells in a highly allergic subject. In many of these cases it seems probable that collapse will be associated with exudation, and areas of caseation may or may not occur.

Whatever be the differences of opinion on the normal pathology of epituberculosis, it is at least generally agreed that it is the glandular component of the primary complex that is largely responsible for the manifestations of epituberculosis and that the affected lobe or segment may be quite other than the one in which the parenchymal component of the complex is situated. Epituberculosis occurs in children because the glandular component is much more prominent in children and perhaps also because of the compressibility of children's bronchi. The effect of the glands on the bronchi, and sometimes even on the trachea, is responsible for the wheeziness and asthma-like breathing which is sometimes observed (Graham & Hutchison, 1947).

These views on the pathogenesis of epituberculosis have been confirmed by bronchoscopic studies (Graham & Hutchison, 1947; Hutchison, 1949; Lemoine, 1951; Rogstad, 1951; Adler & Richards, 1953). Bronchoscopy may occasionally have some therapeutic value when it proves possible to open up the lumen and allow re-expansion of the collapsed area (Morlock & Pinchin, 1933). In most cases this is unsuccessful, possibly because further caseous material exudes from the gland that is eroding through the bronchial wall or because exudation has occurred in the collapsed area of lung.

6. Bronchiectasis after Primary Pulmonary Tuberculosis

It is now generally agreed that bronchiectasis may occur after primary pulmonary tuberculosis, especially when there has been evidence of epituberculosis. But the frequency of this occurrence and its clinical significance is more controversial. It is probable that some of the differences of opinion are due to differences in material. For instance, Macpherson & Lutwyche (1950) found a low incidence of bronchiectasis when they were dealing mainly with an out-patient clinic and did not in most cases perform a bronchogram, whereas Roberts & Blair (1950), who found an incidence of 60%, were analysing subjects ill enough to be admitted to hospital. Other recent British figures are 16% (Richards, 1944) and 53% (Hutchison, 1951). Roberts and Blair in their paper give a useful review of the possible mechanisms involved and conclude that distension by mucus, caseous tissue or secondary infection beyond the bronchial block is probably an important factor. It seems probable that some distortion or widening of the bronchi may occur in a high proportion of patients who have shown segmental or lobar lesions for a prolonged period. Whether this abnormality gives rise to later symptoms will partly depend on its anatomical distribution. In the lower lobe, where drainage is comparatively poor, clinical bronchiectasis is more likely than when the bronchiectasis is in the upper lobe. Williams (1951) has emphasized how little secondary infection may follow this type of bronchiectasis. Brock (1950) describes late manifestations of bronchiectasis in the middle lobe in patients with calcified areas, which suggest that the bronchiectasis originated in a primary infection many years before.

7. Treatment

The problem of whether to treat primary tuberculosis in hospital or at home is not an easy one but in general it is considered that children are best treated at home provided that the social conditions are satisfactory and that this does not involve leaving the child in continued close contact with an infective case. It is regarded as undesirable to separate a child from his home surroundings for long periods if this is avoidable (Miller, 1952). If the child is ill or if there are extensive changes in the radiograph, he should be kept at rest in bed in the first place.

The problem of chemotherapy is a more difficult one. Most investigators have found that chemotherapy has little effect on enlarged hilar or mediastinal glands (Jones & Howard, 1949; Lorber, 1950; Hutchison, 1951; Todd, 1952; Miller, 1952) although it is probably effective on the parenchymal component if this is progressive (Jones & Howard, 1949; McEnery, Sweany & Turner, 1949). It is interesting to speculate why chemotherapy is so ineffective in this particular type of tuberculosis when it is on the whole very successful in, for instance, enlarged cervical glands. It may be that, owing to the degree of hypersensitivity in the child, the glands enlarge and caseate at a very early stage in the disease. However effective the chemotherapy may be on tubercle bacilli that are reached by the drugs, it may have very little effect on lymph glands that have been converted into mere bags of caseous tissue by the time the patient is first seen. Until this caseous tissue has been absorbed or has been discharged into a bronchus, coughed up the trachea and swallowed, the radiographic appearances are likely to persist. It may be concluded that chemotherapy is not in general to be recommended for primary tuberculosis in children unless there is a large parenchymal component, especially if this spreads progressively; or the child is ill with a high temperature; or he is under the age of one year, when the chances of miliary tuberculosis or tuberculous meningitis are much higher. But it is possible that these criteria may be widened by later study. In primary tuberculosis in adolescents or young adults there is a high risk of the later development of post-primary pulmonary tuberculosis, and chemotherapy seems therefore justified in these cases. The question of surgery for primary tuberculosis in the child is a controversial one. Many authorities consider that primary tuberculosis is a benign condition. Later morbidity in most series is comparatively low, though Lincoln (1950) recorded a mortality rate of 23.9% over a 10-year period in New York City. Those holding that the disease is usually benign would resort to surgery only if the illness had run a prolonged course and there was good evidence of a destructive caseous bronchopneumonia confined to a limited area of the lung. Others, notably Dillwyn Thomas and his colleagues at Sully Hospital, Sully, Glamorgan (Thomas, 1952)[1], are impressed with the frequency of later complications and recommend the surgical removal of epituberculous lesions in a number of cases. They even suggest that where there are very much enlarged hilar glands it may be justifiable in certain cases to dissect these out as a prophylactic measure. The soundness of such views will be tested by further experience.

8. Summary and Conclusions

i. Bovine tuberculosis, which was formerly an important problem in the United Kingdom, is now being brought under control by the increasing provision of safe milk. In 1953 over 90% of the marketed milk in England and Wales, and over 99% in Scotland, was either pasteurized or from tuberculin-tested herds. Nevertheless in 1949–50 the MRC National Tuberculin Survey showed that, at the age of five, 20.3% of children in rural areas had positive tuberculin tests, as compared with 9.3% in southern urban areas.

ii. Although the great majority of primary tuberculous lesions are in the lungs, and most of the others in the tonsils or intestines, primary lesions of the skin and mucous membrane are not very rare.

iii. After primary infection, acute disseminated lesions are more common in infants, progressive pulmonary disease in adolescents and young adults. The glandular component is radiographically more obvious in children than in young adults, in whom the appearances are often indistinguishable from post-primary pulmonary disease.

[1] See also Harley, p. 145 of this number of the Bulletin.—Ed.

iv. Erythema nodosum accompanies primary tuberculosis more commonly in Scandinavia than in the United Kingdom.

v. Epituberculosis is a radiographic conception. The underlying pathology may be collapse of a part of the lung from pressure of a gland or from the gland eroding into the bronchus; an exudative inflammatory lesion; a caseous pneumonia; or any combination of these. The frequency with which one or the other predominates is uncertain. The few histological studies have usually indicated an exudative lesion, but bronchoscopic studies have shown erosion of, or pressure on, the bronchus by an enlarged lymph node in a high proportion of cases; probably initial collapse with later exudation is the commonest combination.

vi. Bronchiectasis may occur after primary pulmonary tuberculosis, especially if there has been epituberculosis. The differences in frequency reported probably reflect differences in material. The occurrence of clinical symptoms depends mainly on anatomical site.

vii. Chemotherapy seems to have little effect on enlarged hilar or mediastinal glands but is effective in a progressive parenchymal component. It is also indicated in infants, who run a high risk of disseminated disease, or in ill children. In adolescents or young adults, in whom the parenchymal lesion is dominant, chemotherapy should always be given. Most authorities recommend surgery only for destructive lesions which have run a prolonged course, though certain workers urge early intervention in selected cases.

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DEVELOPMENTS IN THE TREATMENT OF BONE AND JOINT TUBERCULOSIS

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1 Tuberculosis of the spine
2 Tuberculosis of the hip
3 Tuberculosis of the knee
4 Tuberculosis of the shoulder
5 Tuberculosis of the elbow
6 Tuberculosis of the wrist
7 Treatment of tuberculosis of the ankle and of the foot
8 Effect of streptomycin on tuberculous tissues, observed macroscopically and microscopically
9 Summary
References

Chesterton (1913) has stated that real development is not leaving things behind, as on a road, but drawing life from them, as from a root. The application of this principle to the treatment of bone and joint tuberculosis has recently become important because changes are occurring so rapidly that there is danger that the lessons learnt as a result of long experience may be forgotten. The work that was started in Great Britain by Thomas (1875) should be continued, so that rest, open air therapy, good diet and suitable splinting during the acute phase of the disease should still play their part in treatment. By these means, when orthopaedic hospitals became established throughout Great Britain, many patients' lives were saved and much severe crippling was avoided. Great as this improvement was, the patient suffering from skeletal tuberculosis had still much to endure: the duration of treatment was long; there was almost inevitable loss of function of the affected joint; a major operation was often required to stabilize the joint at the end of treatment; and a five-year follow-up showed a mortality of almost 30%. These limitations of successful treatment, affecting as they did both children and adults in the prime of life, were tragic. The problem therefore, when antibiotics became available, was how to retain the value of the old methods and at the same time reduce their disadvantages.

The earliest researches with streptomycin (National Tuberculosis Association: see Riggins & Hinshaw, 1949) showed that it was of great value in the treatment of miliary tuberculosis; reports were also received of its value in the treatment of tuberculous sinuses. These findings were of major importance to orthopaedic surgeons because they removed the principal dangers of the surgical drainage of the affected tissues, a first principle of surgery that had previously not been applicable in the treatment of skeletal tuberculosis, because of the risk of miliary spread or secondary septic sinus formation. Without such surgical drainage or removal of tuberculous necrotic material, abscesses and granulomata were required to heal by recalcification and reossification, a time-consuming and uncertain process. By the removal of granulomata by curettage, a pathway can be opened for invasion of the diseased area by angioblasts and osteoblasts, and free access of the antibiotic to the lesion is made possible. This access of antibiotic to necrotic tuberculous areas is necessarily very limited without surgery, because not only does the tuberculous lesion tend to shut itself off by the formation of fibrous tissue but there is also an accompanying arteritis in the periphery of the lesion (Boyd, 1929). An illustration of this is shown on Plate II, fig. E.

It was therefore decided at Black Notley Hospital, when antibiotics were introduced, to continue to use every available method of constitutional treatment, but also to combine courses of antibiotics with operation into the site of disease. The results are discussed in this paper. It will be convenient to consider each joint separately, but before doing so reference to fig. 1 will show the alteration which has taken place in operative procedures at Black Notley Hospital. It will be seen that, since the introduction of antibiotics in 1949, the number of operations performed has greatly increased, and that the majority of operations now performed are operations into diseased tissues, whilst the number of classical operations for arthrodesis have been reduced.

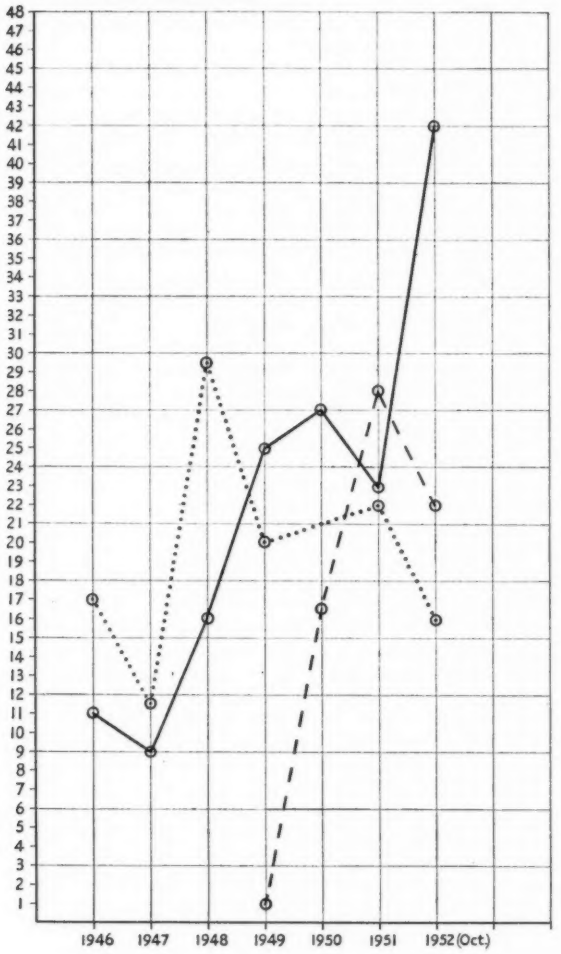
1. Tuberculosis of the Spine

Tuberculosis of the spine is both the most severe and the most frequent form of skeletal tuberculosis. The mortality during a five-year follow-up of patients treated without antibiotics has been approximately 30%, and in addition there has been a significant incidence of deformity and to a less extent of paralysis. The incidence of these two complications depends on the degree of stable ankylosis present at the end of treatment. Table I shows the degree of ankylosis obtained in a series of patients treated conservatively at Black Notley Hospital, and examined, on an average, four years after discharge. This table shows that unsound ankylosis most often occurred in the mid-thoracic and lower thoracic regions of the spine. Fifty-eight per cent of patients with disease in these regions developed an unstable spine. These figures accord with those quoted by Butler (1935) for the incidence of paraplegia; for Butler found that 157 out of 186 patients with paraplegia had tuberculosis of the thoracic spine.

TABLE I. RESULTS OF CONSTITUTIONAL TREATMENT OF TUBERCULOSIS OF THE SPINE IN 131 PATIENTS

Region of spine affected	Stable or bone ankylosis			Fibrous and unstable ankylosis		
	14 years and under	Over 14 years	Total	14 years and under	Over 14 years	Total
Lumbosacral	1	3	4	0	1	1
Lumbar	12	24	36	3	7	10
Dorsolumbar	3	14	17	5	5	10
Lower dorsal and mid-dorsal	7	13	20	12	16	28
Upper dorsal	1	0	1	1	0	1
Cervical	1	1	2	1	0	1
Total	25	55	80	22	29	51

FIG. 1. ALTERATION IN TYPES OF OPERATIONS ON TUBERCULOUS JOINTS, AT BLACK NOTLEY HOSPITAL, SINCE THE INTRODUCTION OF ANTIBIOTICS IN 1949



——— débridement of bone or joint foci

····· operations for joint fusion or displacement osteotomy

— — — — partial capsulectomy and synovectomy

Abscissae: calendar year
Ordinates: number of operations

Since 1949, the number of operations into tuberculous bone has increased and the operation of partial synovectomy has been introduced.

Stability of the spine after constitutional treatment occurred in 53.3% of the children and 65.5% of the adults. The mid-dorsal and lower dorsal regions are the most vulnerable.

The average duration of follow-up was as follows:

patients with bony ankylosis . . 5.4 years,
patients with stable fibrous ankylosis . 5.0 years,
patients with unstable fibrous ankylosis 4.0 years.

One reason for the comparatively poor results of treatment of the thoracic spine was given by Swett, Bennett & Street (1940). In the lumbar, the upper thoracic and the cervical regions, pus can track away from the affected vertebrae. This is not to say that it always does so, a matter which will be mentioned again later. But in the thoracic spine it usually remains pent up as a persistent perispinal abscess. Such pus may in the early stages be under pressure, and so destructive of healthy bone in its neighbourhood. It was shown by Swett and his colleagues that the performance of posterior spinal fusions did little to produce sound healing of the spine if perispinal abscess remained. They therefore recommended the evacuation of pus and granulomatous material from spinal lesions.

Evacuation of tuberculous granulomatous material was already being practised successfully at Black Notley Hospital, before the introduction of antibiotics, for the treatment of peripheral joints such as the ankle, the tarsal, and the wrist (Wilkinson, 1951). This procedure for major joints was considered too dangerous until antibiotics became available, when it was immediately started. At first, patients with tuberculosis of the thoracic spine were treated, but later it was found that progressive disease at other sites might also be due to perivertebral pus, and operations of the same nature have been performed for patients with disease of the lumbar spine. It was found that the performance of such operations, whether on the spine or at other sites of skeletal disease, had a most beneficial effect and almost invariably the progress of bone caries was arrested. It is of great importance therefore that operations should be performed early, before much damage has been done. This is especially necessary in childhood because at that age bone destruction is more rapid.

These arguments in favour of a policy of combined constitutional, antibiotic and operative treatment are reinforced by the comparative failure of treatment without surgery. This observation, it should be noted, is made concerning streptomycin; the use of isonicotinic acid hydrazide (isoniazid) in addition is discussed in section 8. Two series of patients suffering from tuberculosis of the spine were compared: one series consisted of patients treated without antibiotics, the other with. A number of patients suffering from tuberculosis of the thoracic and lumbar spine made up each series (see Table II).

TABLE II. COMPARISON OF RESULTS IN TWO SERIES OF PATIENTS TREATED FOR TUBERCULOSIS OF THE SPINE BY CONSTITUTIONAL TREATMENT, WITH AND WITHOUT THE ADDITION OF STREPTOMYCIN

	Number of patients	Duration of treatment (months)	Radiographic appearance approximately 1 year after discharge		
			Unsound ankylosis	Sound fibrous ankylosis	Bony ankylosis
Lumbar spine					
With streptomycin .	25	12.4	1	5	4
Without streptomycin	30	13.0	1	14	8
Thoracic spine					
With streptomycin .	21	11.9	2	6	3
Without streptomycin	30	13.7	6	10	3

It should be noted that the number of patients treated with antibiotics followed up at the time that Table II was compiled was not large, but was sufficient to show that streptomycin by itself had had no remarkable effect in reducing the duration of treatment or improving the degree of stability. It should be noted that, because patients who received major operative treatment are omitted from this table, the group treated with streptomycin does not contain many of the patients with the worst type of disease, who were operated on under the protection of streptomycin. If these patients had not been treated by operation and had been included in the group suffering from tuberculosis of the thoracic spine who had been treated with streptomycin, the figures for this group would have been less favourable.

Up to the present time 28 patients have been operated upon for persistent perispinal abscess in the thoracic region. The duration of treatment has averaged 9.4 months, but among this number of patients were some readmissions who might otherwise have required longer treatment. At present it is my normal practice to operate after preliminary constitutional treatment and antibiotic treatment for three or four months, and to discharge the patient home four or five months after operation. A spinal brace is worn for a few months after discharge. Many have returned to their former employment within a few months of their discharge from hospital. Two patients have had slight reactivation of the disease at the site of the lesion: these were the first two patients operated upon when the supply of streptomycin was scanty, and the operation was performed late in the disease. When possible, cancellous bone chips have been packed into the curetted area. Stability of the spine has been favoured by the results of this method of treatment. Plate II (figs. F, G and H) shows, respectively, antero-posterior and lateral views of thoracic spine of patient with perispinal abscess, and a lateral view of the lesion two-and-a-half years after operation.

Eight children suffering from tuberculosis of the spine have also been treated by similar methods. Plate III (figs. J, K, L and M) shows, respectively, antero-posterior and lateral views, on admission, and one year later, of tuberculosis of the 10th, 11th and 12th vertebrae in one of these children. As experience has been gained operation has been carried out earlier with increasing benefit.

The majority of patients operated on by these methods have been suffering from tuberculosis of the dorsal spine, a situation where persistent granulomata are found, and in which the prognosis is known to be the worst. It has been observed, however, that some patients with tuberculosis of the lumbar vertebrae without psoas abscess formation have progressed unfavourably and, on exploration of the lesion by the posterior transversectomy approach, pus has been found. It has been my practice recently, therefore, to perform this operation on patients with lumbar spinal disease in whom progressive bone destruction is occurring in spite of full constitutional and antibiotic treatment.

2. Tuberculosis of the Hip

Formerly tuberculosis of the hip in childhood was treated conservatively for approximately two years and afterwards stabilization by operation was performed. The treatment of tuberculosis of the hip in adults was similar but the duration of conservative treatment was less. With the introduction of antibiotics the duration of constitutional treatment before arthrodesis has been considerably reduced. At present a period of approximately four to nine months' treatment is considered sufficient according to the age and condition of the patient. Much more remarkable has been the change in the prognosis for the restoration of function. Before the introduction of antibiotics this was very poor.

Recovery with function from tuberculosis of the hip in childhood can be obtained in a proportion of patients by means of full constitutional treatment and antibiotics alone But by these means, unaided by surgery, functional recovery is often incomplete and uncertain: incomplete because moderate limitation of movement may persist, and uncertain because the disease may still progress to destruction of the joint in a proportion of the patients. If, however, partial synovectomy is performed during the course of treatment, recovery is accelerated and becomes more complete. The state of these joints observed at operation is described in section 8. The value of partial synovectomy can be demonstrated: theoretically its value is supported by the work of Key (1925), who found that after synovectomy in animals a fresh synovial membrane is rapidly re-formed. Perhaps a synovial membrane that is the seat of tuberculosis can be replaced by healthier tissue if the patient is under antibiotic treatment; or perhaps the removal of a portion of diseased synovial tissue, in which blood vessels are partially obliterated, opens the way to revascularization of the highly vulnerable and essential subchondral bone. Whatever may be the reason the results are convincing. Up to the present 24 children, suffering from tuberculosis of the hip, have had a partial synovectomy, accompanied whenever necessary by curettage of obvious necrotic foci in bone. The average duration of treatment has been 11.2 months. Recovery with good function has been obtained in 20 children. None of these patients has relapsed after discharge from hospital. The average period of observation of patients after discharge is approximately two years. Plate IV (figs. N, O and P) illustrates the results of synovectomy for tuberculosis of the hip in a boy of seven. Figure N is a radiograph of the hip, showing the condition on admission, fig. O shows the condition one month after discharge, and fig. P is a photograph of this patient taken on discharge, showing range of movement achieved.

The treatment of tuberculosis of the hip in adults is being tried on similar lines, but with less success, perhaps because adult patients are not usually admitted to a tuberculosis orthopaedic hospital until some joint destruction is already present.

3. Tuberculosis of the Knee

Before the introduction of antibiotics the standard treatment of tuberculosis of the knee in adults was constitutional treatment followed by arthrodesis. In children the disease could be cured by constitutional treatment, and function returned in some. In a series reported by Mortens (1948), 32% of children recovered with a useful range of movement. The duration of treatment of children was approximately 18 months and of adults a year or more. After the introduction of antibiotics the methods used for tuberculosis of the hip in children were also introduced for tuberculosis of the knee, except that partial synovectomy was omitted in those patients whose response to antibiotics was reassuring. The omission of synovectomy seemed reasonable in a form of the disease in which recovery with function had formerly been possible: but for disease of adults whose prognosis for recovery of

RELATIONSHIP BETWEEN HOST CELL AND PARASITE IN TUBERCULOSIS

(FIGS. A, B)

G. B. Mackaness

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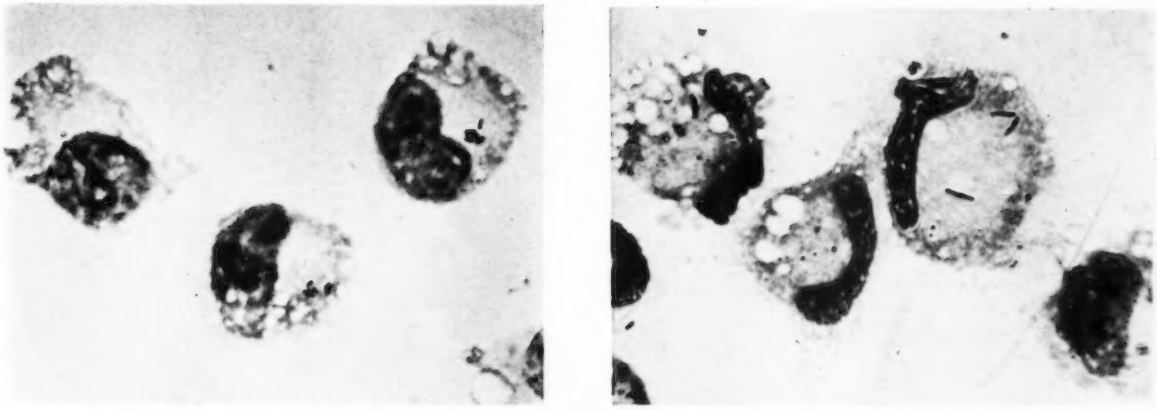

FIGS. A, B. Photomicrographs of stained monocyte cultures fixed 6 and 36 hours, respectively, after commencement of incubation. They show early growth of individual tubercle bacilli (Branch strain) in monocytes obtained from rabbit immunized with living bacilli of the virulent human type H37Rv

(Stain : Ziehl-Neelsen methylene blue ; magnification × 1,400)

SOME EXPERIMENTAL APPROACHES TO THE TUBERCULOSIS PROBLEM

(FIGS. C, D)

R. J. W. Rees

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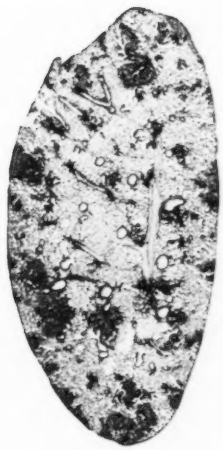

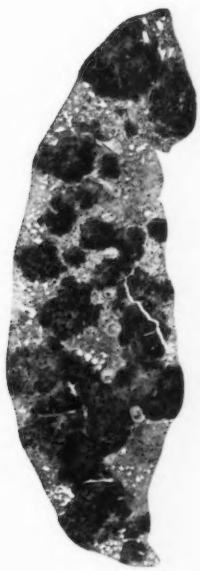

Hart & Rees (1950) by permission of the Lancet

FIG. C. Section through a lobe of the lung from a mouse with a stable chronic tuberculous infection, showing small discrete lesions

FIG. D. The same type of infection after cortisone treatment, showing massive, partially coalescent necrotic lesions

(Stain : haematoxylin and eosin ; magnification × 4)

DEVELOPMENTS IN THE TREATMENT OF BONE AND JOINT TUBERCULOSIS

(FIGS. E—H)

M. C. Wilkinson

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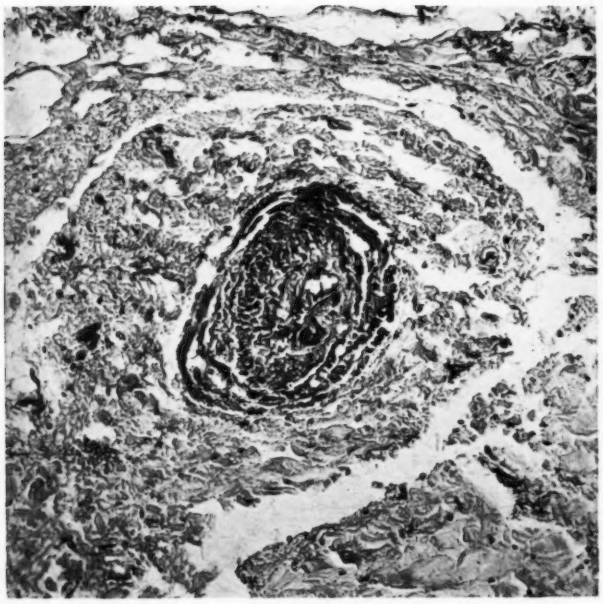

FIG. E. Microscopic section of tuberculous material curetted from tarsus. Obliteration of an artery is seen

(magnification × 130)

FIG. F. Antero-posterior view of thoracic spine of patient with perispinal abscess. Patient treated by costotransversectomy of 9th and 10th left ribs, and abscess curetted

FIG. G. Lateral view of thoracic spine shown in fig. F

FIG. H. Lateral view of lesion, seen in figs. F and G, two-and-a-half years after operation, showing bony ankylosis

FIGS. J, K. Antero-posterior and lateral views of tuberculosis of 10th, 11th and 12th vertebrae in a child aged three. Costotransversectomy and drainage of abscess performed one month after admission

FIGS. L, M. Radiographs of lesion seen in figs. J and K, one year later, showing sound bony ankylosis. Child was discharged 13 months after admission

Tuberculosis of right hip in a boy of seven. Patient given course of streptomycin for 90 days; partial synovectomy performed two months after admission; diagnosis confirmed. Patient discharged after nine months of treatment, with full range of movement

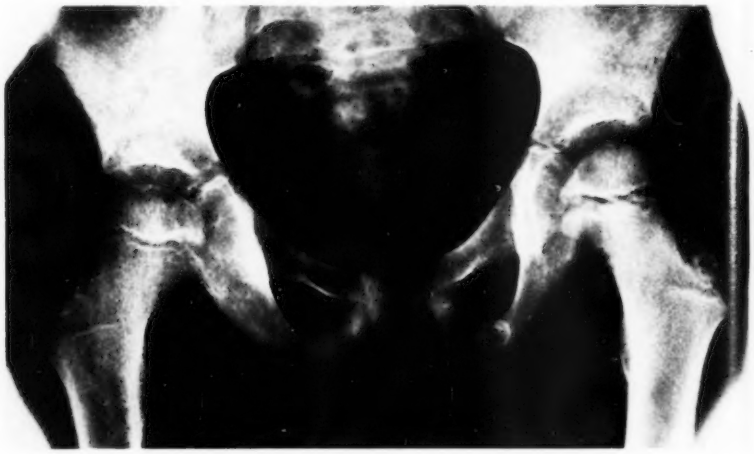

FIG. N. Radiograph of hip, taken on admission

FIG. O. Radiograph of hip, taken one month after discharge

FIG. P. Photograph of patient, showing range of movement after treatment

function had previously been so poor, every possible means of therapy seemed needed. Fifteen adult patients have been treated by these methods: 13 have recovered with a useful range of movement, of approximately 90°; the average duration of treatment of these patients has been 6.7 months. This method of treatment has been possible only for patients who were admitted before extensive damage to the joint had occurred. Similar satisfactory results were obtained with children.

4. Tuberculosis of the Shoulder

It is generally agreed that a pseudarthrosis with movement is more necessary in the upper limb than the lower. Whereas arthrodesis is an acceptable result in the lower limb if joint destruction has taken place before admission to hospital, every effort should be made to recover movement in the upper, even though some damage to the joint has already occurred. Unfortunately gross destruction of joints is too often present when adult patients are admitted. Partial synovectomy with curettage of major necrotic foci may result in a comfortable joint with a moderate range of movement. Patients who have not suffered articular destruction can recover with a full range of movement of the shoulder.

5. Tuberculosis of the Elbow

The treatment for tuberculosis of the elbow follows the same pattern as that for tuberculosis of the shoulder. In the shoulder, the major necrotic lesion requiring curettage has most often been found in the head of the humerus; at the elbow, the situation is usually the junction of the olecranon with the upper end of the ulnar shaft. The disease elsewhere is predominantly synovial; gross cartilaginous destruction occurs later with or without absorption of the bony articular surfaces. The preliminary treatment with constitutional measures and antibiotics usually lasts two months. Access to the joint has been by a posterior incision; the olecranon process is removed with the insertion of the triceps attached and is reflected upwards with the triceps. At the end of the operation the olecranon is pegged back into position. A light posterior gutter splint is worn after the operation for the first few weeks; it is removed for gradually increasing periods as early as possible to allow attempts at active movement. Such operative treatment may not be required for tuberculosis of the elbow in children.

By these means it is possible in the majority of patients to obtain ranges of movement from 70° of flexion to 150° of extension. If there is much limitation of pronation and supination, excision of the radial head should be performed. Children almost uniformly recover, with full range of movement.

6. Tuberculosis of the Wrist

It is generally agreed that there may be good function of the hand even though the wrist joint is fixed. The author, however, has only rarely employed posterior fusion of the wrist. Tuberculosis of the wrist is a misnomer because the disease starts in the carpometacarpal joints, and involves chiefly the carpus. Posterior synovectomy should be performed with the removal of necrotic material from the carpus. A considerable amount of the carpus may be lost without grossly affecting either function or the cosmetic appearance.

7. Treatment of Tuberculosis of the Ankle and of the Foot

It has been mentioned above that satisfactory results were being obtained in the treatment of tuberculosis of the carpus and of the foot by curettage and bone grafting, even before the introduction of antibiotics. Since then it has been possible to reduce materially the pre-operative period of treatment, so that operation is now performed approximately two months after the admission of the patient to hospital; the total duration of treatment has been reduced to approximately six months. After curettage of the tarsal bones cancellous bone chips are used to supplement the defect; after excision of the articular surfaces of the ankle joint a graft from the anterior surface of the tibia is slid down into the astragalus. Stable feet with good function result from these methods and, though it would seem quite justifiable to try partial synovectomy for suitable patients with tuberculosis of the ankle, the author is unable to report any experience of such a method of treatment.

8. Effect of Streptomycin on Tuberculous Tissues, Observed Macroscopically and Microscopically

Antibiotic treatment of active tuberculous joints is usually accompanied by subsidence of acute symptoms and signs. This may be a genuine improvement but biopsy of the joint often reveals gross disease in spite of disarming external appearances. It has been possible to assess the effects of antibacterial agents in a series of patients treated by operation. The antibiotic used for the majority of patients was streptomycin; more recently, combined streptomycin and isoniazid have been used but attempts to assess the combined therapeutic effect are still incomplete. Macroscopic and microscopic examinations have been made on specimens removed at operation after courses of antibiotics of varying amounts. It was found on microscopical examination that the tubercles underwent recession: the degree of recession varied with the amount of streptomycin treatment which had been given, and according to the nature of the tissue involved. The effect of streptomycin is more marked in synovial tissues than in bone, and is greater after a course of treatment lasting 90 days than after shorter courses. Even after treatment for 90 days and even in the synovial tissues, tuberculous changes can still be demonstrated in the majority of patients. The findings have been enumerated elsewhere (Wilkinson, 1954), and here they will only be summarized briefly.

After 90 days' treatment the microscopical appearance of 27 out of 36 patients still showed tuberculous changes: for periods of treatment of less than 90 days the microscopical appearances of tuberculosis were still present in 28 out of 30 patients.

The differences between the effect of streptomycin on bone and on synovial membrane were compared. It was found that after treatment for 90 days 14 patients out of 22 still showed tuberculous changes in the synovial membrane; in 8, no specific changes were seen. In the bone of 14 patients treated for a similar length of time tuberculous changes were present in all but one.

The effects of streptomycin are therefore more marked on synovial tissues than on bone; a small number of examinations were made of patients who had received courses of isoniazid only, but no material difference was seen from those treated with streptomycin. Nevertheless, the use of isoniazid with or without streptomycin must be closely studied, because

Dick (1953) has published interesting researches on its use in the treatment of renal tuberculosis, which might considerably influence the treatment of joint tuberculosis. The following observations were reported by Dick: tubercles were observed to undergo recession after isoniazid treatment; increased vascularity was found at the periphery of the lesion; some absorption of caseous material occurred, and healing was observed to occur without fibrosis. The healing that occurs as the result of streptomycin treatment is accompanied by fibrosis; an agent which produces healing without fibrosis is bound to be of interest to a surgeon concerned with the treatment of joints.

9. Summary

A new era in the treatment of skeletal tuberculosis has begun. The antibiotic drugs are of themselves valuable, but are prevented from exercising their curative function in established tuberculous lesions by tissue changes round the lesion. Their value is considerably enhanced by surgical measures designed to open a path into the diseased tissues. These surgical measures are of themselves valuable therapeutic methods in the treatment of skeletal tuberculosis. Before the introduction of antibiotics they were unsafe. Surgical and antibiotic treatment are therefore complementary. Constitutional treatment remains essential to ensure safety in operating and permanently good results. By a combination of these methods, the duration of treatment can be remarkably reduced. Function can be restored if treatment has been started before joint destruction has occurred. Early diagnosis has become of great importance. The disease need no longer be a crippling disease.

ACKNOWLEDGEMENTS

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CLINICAL USE OF ANTIBACTERIAL DRUGS IN PULMONARY TUBERCULOSIS

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1 Clinical importance of drug resistance
2 Effectiveness of the commonly used antibacterial drugs in pulmonary tuberculosis
3 Some less frequently used antibacterial drugs
4 Choice of combinations of antibacterial drugs
a General considerations
b Factors affecting choice of drugs in the individual case
5 Indications for antibacterial treatment in pulmonary tuberculosis
6 Summary
References

The use of antibacterial drugs has become so essential a part of the treatment of tuberculosis that it is a little difficult to realize that they have been in general use for no more than seven years. It is the aim of this paper to discuss the practical problems of the antibacterial treatment of pulmonary tuberculosis in the light of such principles as seem at present to be reliably established, and also in relation to the general body of clinical knowledge about the course and management of this disease. Although, as described by Fox (see his paper in this number of the Bulletin, p. 108), large-scale therapeutic trials have been conducted to provide reliable data upon which rules for the clinical application of these drugs may be based, many problems remain unsolved. This is not surprising, since the clinical assessment of the value of any form of treatment in a long-continued and chronic disease must inevitably be slow; and in the case of the antibacterial treatment of tuberculosis, further delay is entailed by the need for careful correlation of clinical results with laboratory studies of bacterial resistance, the estimation of which is time-consuming. In addition, with three drugs of accepted value in general use and several others in occasional use, there are many possible combinations of drugs in various dosages which present an a priori case for clinical investigation. For all these reasons, practical policies in antibacterial treatment of tuberculosis, even with the drugs which are in general use, are still changing; and, of course, it is probable that effective new agents will be discovered in the future. Hence, some at least of the views expressed in this paper must be regarded as provisional.

1. Clinical Importance of Drug Resistance

The general problems of resistance to antibacterial drugs in tuberculosis are discussed by Mitchison elsewhere in this Bulletin (p. 115). Clinically, when streptomycin first became available for general use, the acquisition of drug resistance by the infecting bacilli was very soon recognized as a limiting factor. The next important step in the evolution of practical antibacterial treatment was the discovery that the combination of *p*-aminosalicylic acid (PAS), usually given in the form of its sodium salt (sodium PAS), with streptomycin greatly delays the emergence of resistant strains of bacilli. This increased the permissible scope of antibacterial treatment very considerably; for with streptomycin alone it was clear that antibacterial treatment could probably be given effectively to a patient with pulmonary tuberculosis only once, and for a relatively limited period, during the course of what might be a long and fluctuating struggle with the disease. The introduction of isonicotinic acid hydrazide (isoniazid), and the demonstration that it has an antibacterial activity in tuberculosis of similar potency to that of streptomycin, and that the combination of it with either streptomycin or PAS is effective in limiting the emergence of resistant strains to either drug, still further increased the latitude permissible to the clinician in the use of antibacterial treatment; for, with three effective drugs available, if a patient's strain of tubercle bacilli becomes resistant to one drug there still remain two which, in combination, are effective both clinically and in limiting the rate of emergence of resistant strains. Another consideration which has encouraged the use of antibacterial treatment in a wider range of types of disease, and for longer periods, is that the data available about the emergence of resistant strains have been derived for the most part from patients having the sort of disease which is recognized to be most favourable to the development of bacterial resistance—acute disease with extensive caseation and cavitation. It is highly probable that the danger of the emergence of resistant strains in less extensive and active lesions is considerably less. All these considerations have tended to encourage longer periods of treatment of patients with a wider range of types of disease.

Nevertheless, these considerations must not lull the clinician into complacency about drug resistance; and the tendency to use longer periods of treatment with antibacterial drugs increases the importance of using them in such a way as to minimize the danger of the emergence of resistant strains. This means that, in general, two antibacterial agents, to both of which the patient's tubercle bacilli are fully sensitive, should be used in combination. For the individual patient, such a procedure is essential if he is to derive full benefit from antibacterial treatment; if the bacilli are resistant to one of the drugs administered, not only will the patient derive no benefit from the administration of that drug (a matter of relatively little importance), but also the bacilli will behave towards the other drug as if it were being given alone, and resistance to it also will be very likely to arise if the combination is administered for a long period (Turnbull, Wallace, Stewart & Crofton, 1953; Medical Research Council, 1953b). If this occurs, the patient will be left with only one of the most effective drugs available to him, with no very satisfactory method of limiting the possibility of the emergence of strains resistant to it also should the occasion for its use arise. From the point of view of the community in general, patients who, after this sort of unsatisfactory antibacterial treatment, become chronic excretors of drug-resistant tubercle bacilli, are a great danger, since all available evidence suggests that drug resistance tends to be a fixed

characteristic of a strain of bacilli. There are already a number of reports of patients who have been primarily infected with tubercle bacilli resistant to one or more of the commonly used antibacterial drugs, presumably as a result of the unsuccessful treatment of the person who was the source of their infection.

2. Effectiveness of the Commonly Used Antibacterial Drugs in Pulmonary Tuberculosis

Of the three drugs in common use, streptomycin and isoniazid seem to be about equally effective in pulmonary tuberculosis when judged by such criteria as reduction of fever, control of symptoms, and improvement in the radiographic appearance of the lungs. PAS is less effective in these respects. Any pair chosen from these three drugs is clinically effective. There is some evidence that streptomycin and isoniazid together are a little more effective than streptomycin and PAS, or isoniazid and PAS; the latter two combinations seem to be of about equal clinical effectiveness (Medical Research Council, 1953c). These statements apply to the usually administered doses of 1 g. of streptomycin daily by intramuscular injection, 100 mg. twice daily of isoniazid by mouth, and 5 g. four times daily of sodium PAS by mouth, all these doses being those for an adult. There is considerable evidence that the combination of 1 g. of streptomycin two or three times a week, with PAS daily, is very little inferior in clinical effect to streptomycin daily with PAS daily (Tempel, Hughes, Mardis, Towbin & Dye, 1951; Dye, 1952).

Toxic effects, though rarely serious, may interrupt the normal course of treatment, and the possibility of their occurrence may influence the physician in the choice of treatment.

The most important toxic effects of streptomycin are on the eighth nerve, particularly its vestibular division. The most common symptoms are dizziness, which may amount to vertigo, and unsteadiness in walking. They are more frequent in older patients, and appear to be a direct toxic effect of the drug, and not due to sensitization. Fortunately, the damage is not usually progressive after the administration of the drug is stopped, and its functional effect steadily diminishes as other mechanisms of equilibration take over the function of the damaged labyrinth. Patients who in the early days of streptomycin treatment received doses far higher than those at present administered, and who suffered gross labyrinthine damage, nevertheless compensated eventually, so that within six months or a year they were able to move about freely and without obvious disability except in complete darkness. With streptomycin, the incidence of serious damage to the auditory division of the eighth nerve is very low. Dihydrostreptomycin was found to cause considerably less damage to vestibular function, and accordingly was introduced into clinical practice. However, it has been shown to cause a significant incidence of nerve deafness which, in some cases, has proved to be progressive even though the administration of the drug is stopped (O'Connor, Christie & Howlett, 1951; Don & Gregory, 1952). This nerve deafness is irreversible, and of course there can be no satisfactory compensation for loss of hearing. Accordingly, it seems far preferable to accept the very slight risk of labyrinthine damage which is entailed by the commonly used levels of streptomycin dosage, rather than to run a numerically smaller risk of nerve deafness from dihydrostreptomycin. The only other important toxic effects of streptomycin are sensitivity reactions, which may take the form of drug rashes, drug fever, and, rarely, generalized reactions in which fever is accompanied by such manifestations as lymphadenopathy and arthropathy. These sensitivity reactions include a contact dermatitis which affects those who administer the drug rather than the recipients of it, and necessitates special care in the technique of injection to minimize the chances of contamination of the hands of the nurse (Crofton & Foreman, 1948; Ministry of Health, 1953). Streptomycin sulphate is to be preferred to the streptomycin calcium chloride complex, as it causes less pain on intramuscular injection. The principal direct toxic effects of PAS are on the alimentary system—nausea, vomiting, abdominal discomfort, anorexia and diarrhoea. They tend to be rather more troublesome the larger the dose of the drug, but most patients are able to tolerate the full dose of 20 g. daily of sodium PAS. Sensitivity reactions, with skin rashes and constitutional symptoms similar to those observed with streptomycin, also occur. Disturbance of serum electrolytes, with low potassium level, have also been reported, but are probably in the main attributable to the increase in sodium intake entailed by the long-continued administration of the sodium salt of PAS. By comparison, the toxic effects of isoniazid are relatively few. Although symptoms referable to the central nervous system were reported when the drug was first used, they are excessively rare in the doses being used at present.

3. Some Less Frequently Used Antibacterial Drugs

Of other antibacterial drugs that have been used in the treatment of tuberculosis, the sulphones, the thiosemicarbazones, and neomycin hardly enter into current clinical practice. The sulphones have proved to be toxic in relation to their rather feeble antibacterial activity. Although the thiosemicarbazones have a strong antibacterial effect, both in vitro and in the experimental animal, their clinical effectiveness seems to be approximately equivalent to that of PAS, while their toxic effects are troublesome. Their activity in limiting the emergence of resistant bacteria, when they are given in combination with streptomycin, is unsatisfactory (Greenberg, 1952). Neomycin, isolated in 1949 from *Streptomyces fradiae* (Waksman & Lechevalier, 1949; Waksman, Hutchison & Katz, 1949) is very active in vitro against the tubercle bacillus, but has serious toxic effects which make it unsuitable for clinical use (Carr, Pfuetze, Brown, Douglass & Karlson, 1951).

Viomycin, isolated in 1950 from *Streptomyces floridae* or *puniceus* (Finlay *et al.* 1951; Bartz, Ehrlich, Mold, Penner & Smith, 1951), appears to have an activity against the tubercle bacillus comparable to that of streptomycin, though slightly less. It is less toxic than neomycin (Werner, Tompsett, Muschenheim & McDermott, 1951), and has proved suitable for clinical use in patients whose bacilli are resistant to other antibacterial agents. It is more toxic than streptomycin, the toxic effects being on both divisions of the eighth nerve, on the kidneys, causing albuminuria and cylindruria, and on the electrolyte balance. Oxytetracycline (terramycin), while having a bacteriostatic effect on tubercle bacilli only in relatively high concentrations (Hobby, Lenert, Donikian & Pikula, 1951), seems to be effective in limiting the rate of emergence of resistant strains when it is given in combination

with streptomycin (Miller, Sands, Walker, Dye & Tempel, 1952; Rothstein & Johnson, 1952; Schwartz & Moyer, 1952). For this purpose it has been given in doses as high as 5 g. daily, and this is very liable to give rise to unpleasant side-effects, especially on the gastrointestinal tract, so that some patients are unable to tolerate it. Recently, small-scale investigations have suggested that smaller doses of oxytetracycline may be effective; Miller, Sands, Gregory, Hightower, Weiser & Tempel (1954) suggest that the optimal dosage lies between 2 g. and 5 g. daily, while Rothstein & Johnson (1954) claim that as little as 1 g. daily may be effective with intermittent administration of streptomycin. In addition to the present uncertainty about the optimal dosage, oxytetracycline has the disadvantage of high cost. Its use is therefore justifiable only when no other drug is available to combine with streptomycin. The combination clearly needs more investigation. Conceivably, if the combination of isoniazid and PAS is widely used, there may be an increasing number of patients whose tubercle bacilli have become resistant to both these drugs; in such cases a combination of streptomycin and terramycin might be useful.

4. Choice of Combinations of Antibacterial Drugs

a. General Considerations

Until isoniazid became available, together with the basic data necessary for its clinical use (Medical Research Council, 1953a, 1953b, 1953c), the combination of streptomycin and PAS, in various dosages, was the most useful antibacterial measure in tuberculosis. In younger patients, in whom the danger of damage to the vestibular apparatus was small, and particularly in acute forms of tuberculosis in which a rapid effect was desirable, 1 g. daily of streptomycin sulphate by intramuscular injection, combined with 5 g. four times a day of sodium PAS by mouth, was the most effective treatment. The need for the high dosage of PAS was demonstrated in one of the Medical Research Council (MRC) trials, in which it was shown that this dose was considerably more effective than either 10 g. or 5 g. daily in limiting the emergence of streptomycin-resistant strains (Medical Research Council, 1952). It is, of course, possible that somewhat smaller dosage in the range between 20 g. and 10 g. daily might be effective in this respect, but precise comparative data are not available on this question. In patients in whom the need for a rapid effect was less, and in older patients in whom the vestibular apparatus is more vulnerable to streptomycin, 1 g. of streptomycin two or three times weekly was preferred.

Isoniazid and streptomycin, both given daily, seem, as already stated, to be the most effective combination of drugs now available for the treatment of pulmonary tuberculosis. The toxicity of the combination is, for practical purposes, that of the streptomycin alone. The rate of emergence of resistant strains to either of these drugs when they are given together is low. The one disadvantage of this combination is that if the strain of tubercle bacilli infecting a patient to whom it is given becomes resistant to one of the drugs, it is likely to become resistant also to the other, and thus the two drugs with the most potent antibacterial action will become ineffective for that patient. The combination of isoniazid daily with streptomycin intermittently has been shown to be less effective in diminishing the rate of emergence of isoniazid-resistant bacilli; in the MRC investigation, 9% of patients to whom 100 mg. of isoniazid twice daily was given, with 1 g. of streptomycin twice weekly, produced isoniazid-resistant bacteria after three months of treatment (Medical Research Council, 1953c); but these results have not yet been confirmed in other investigations. Nevertheless, it seems wise to avoid giving streptomycin intermittently with isoniazid. If for any reason, such as the age of the patient, or the convenience of giving two or three injections only per week to a patient being treated in his home, intermittent administration of streptomycin is desirable, it should be accompanied by PAS rather than isoniazid.

Isoniazid and PAS form an attractive combination, since they can both be given by mouth. Their toxicity is, for practical purposes, that of the PAS alone. The combination of 100 mg. of isoniazid twice daily, with 20 g. of PAS daily, has been shown to be one of the best, if not the best, of all drug combinations in minimizing the danger of the emergence of resistant strains. In the MRC trial (Medical Research Council, 1953c), only 1% of patients treated in this way had produced strains resistant to PAS at the end of three months' treatment, and no patient had produced strains resistant to isoniazid. Even in patients receiving only 10 g. daily of PAS with isoniazid, the percentage producing strains resistant to isoniazid at the end of three months was only two, and the percentage producing strains resistant to PAS was also two. It appears from this evidence that rather less than 20 g. daily of PAS may be adequate in combination with isoniazid for the reduction of liability to bacterial resistance. The clinical effectiveness of the combination of isoniazid and PAS, as judged by changes in symptoms and in radiographic appearance, seemed slightly less than that of streptomycin and isoniazid, but the differences were not statistically significant. The combination of isoniazid and PAS seems likely to be used widely in the treatment of pulmonary tuberculosis because of the convenience of administration of two drugs by mouth.

It has been shown recently that tubercle bacilli highly resistant to isoniazid may have low pathogenicity for laboratory animals (Steenken & Wolinsky, 1953; Barnett, Bushby & Mitchison, 1953). However, it is improbable that this phenomenon is of clinical importance. A laboratory report that a strain of bacilli has resistance indicates only that a small proportion of the bacilli are resistant; moreover, the low pathogenicity has up to now been reported only for bacilli of very high resistance, which are uncommonly encountered clinically. Bacilli of the lower level of resistance which more usually develops in patients undergoing isoniazid treatment have been shown to be normally pathogenic for laboratory animals. Hence, this interesting observation does not justify any exception to the general rule that antibacterial treatment in pulmonary tuberculosis must be conducted with combinations of drugs that minimize the risk of the emergence of drug-resistant strains of tubercle bacilli.

b. Factors Affecting Choice of Drugs in the Individual Case

At present, a patient who is not known to have been in close contact with a person who has, in the past, undergone antibacterial treatment for tuberculosis, nor himself has previously received such treatment, may with reasonable certainty be assumed to be infected with bacilli which are sensitive to the commonly used antibacterial agents. Ideally, sensitivity tests should be done before starting treatment, but the amount of laboratory work necessary makes this a counsel of perfection for all but the most favoured

communities. In practice, if a patient's history gives no reason to suspect that the bacilli might be resistant, treatment may be started on the assumption that they are sensitive.

When it seems likely that antibacterial drugs will be the principal form of treatment in a case of pulmonary tuberculosis, and there are no complicating factors, the choice rests between the combination of streptomycin daily with isoniazid, streptomycin daily with PAS, and streptomycin two or three times a week with PAS. For reasons indicated above, it seems best to start with streptomycin and PAS, the decision between daily and intermittent streptomycin depending upon the acuteness of the disease and the age of the patient. Certainly, where the disease is acute, with extensive cavitation and caseation, streptomycin and PAS should be the first choice, since this is the type of case in which the danger of the emergence of resistant strains of bacilli is highest, and the reason for avoiding the simultaneous administration of the two most effective drugs is therefore strongest. Of course, a few patients prove so intolerant of PAS that isoniazid has to be substituted. In older patients, a combination of either PAS with streptomycin two or three times a week, or PAS with isoniazid, should be chosen. If circumstances are such that treatment must be conducted in the patient's home, the combination of isoniazid with PAS presents obvious advantages, but streptomycin two or three times weekly with PAS is also generally practicable. It has the advantage that it ensures that the patient is visited frequently by a doctor or nurse.

If a patient has previously received treatment with a combination of antibacterial drugs, sensitivity tests should be carried out, and the results known before starting treatment. If he has, in the past, received treatment with one drug alone, urgent treatment may be planned on the assumption that the bacilli are likely to be resistant to that drug. This means that the combination of the two drugs which he has not previously received should be chosen. Similarly, if the patient is known to have been in contact with a person who has received antibacterial treatment, and it seems at all possible that his infection was derived from that person, preliminary sensitivity tests are highly desirable. The results of these tests will influence the choice of treatment in obvious ways. A rapid and reliable "screening" test for significant levels of resistance of tubercle bacilli to the more commonly used drugs has not yet been developed, but would be very valuable. There are few patients, however, who will come to harm if kept at rest in bed, while awaiting the result of a sensitivity test; much harm may be done by the wrong choice of antibacterial drugs.

A point of occasional importance is that high blood levels of streptomycin may result, in patients with renal damage, from failure of glomerular excretion of the drug; where there is nitrogen retention, as shown by a high level of urea in the blood, injected streptomycin will also be retained abnormally. This situation is most likely to arise, in patients with chronic forms of pulmonary tuberculosis, as a result of amyloid disease. If, in such a case, streptomycin is being administered, its concentration in the blood should be estimated in order to ascertain that the doses given are not producing a potentially toxic concentration. In patients with severe renal damage, reduced dosage of streptomycin should be used from the beginning. This difficulty does not arise with isoniazid and PAS.

5. Indications for Antibacterial Treatment in Pulmonary Tuberculosis

Full discussion of the place of antibacterial treatment and of its integration with other forms of treatment in pulmonary tuberculosis is not possible in limited space; a few general observations only can be made. The most important effects of antibacterial drugs are upon the pneumonic forms of tuberculosis, and upon active tuberculosis of the bronchi; and foci of disease of pneumonic type, active bronchial tuberculosis, or both these types of disease, are probably present in parts of the lungs of all patients showing clinical evidence of activity of the disease. Apart from the emergence of drug-resistant strains of bacilli, the chief obstacles to the complete cure of pulmonary tuberculosis by antibacterial drugs are such mechanical factors as cavities which, for one reason or another, cannot be closed by the natural reparative processes; large caseous foci which, though they may become encapsulated by fibrous tissue, may subsequently liquefy, forming cavities and leading to the risk of bronchogenic spread of disease; and bronchial stenosis consequent upon the healing of severe bronchial tuberculosis. It therefore follows that, in cases of active pulmonary tuberculosis, careful judgement is necessary in the proper combination of antibacterial treatment with other measures such as collapse therapy and resection. Combinations of procedures which are now practicable are so numerous that it is impossible to hope for statistical appraisal of all of them, and, especially in a disease so various in its manifestations and natural course, judgement must be based not only upon the established results of statistical studies concerning single methods of treatment of specially defined types of the disease, but also upon clinical experience.

A few examples serve to illustrate the variety of problems which may arise. In a patient with acute pneumonic tuberculosis involving both lungs, with or without cavities, it is clear that the first line of attack must be through the antibacterial drugs and rest in bed. Sooner or later, however, a stage is likely to be reached at which it is obvious that no matter how long treatment is continued residual cavities are likely to persist. At this stage, the best policy is to proceed with some form of collapse treatment as soon as the activity of the disease has been sufficiently controlled, and the patient's general health sufficiently improved; beyond this point delay in instituting collapse treatment is time wasted. The form of collapse therapy must be decided according to the circumstances of the individual patient: pneumothorax, phrenic paralysis and pneumoperitoneum, thoracoplasty and equivalent plombage procedures such as the extraperiosteofascial apicolysis with plombage of Cleland (Lucas & Cleland, 1950), or combinations of these procedures, being used according to the individual indications. If the residual cavitated disease happens to be appropriately localized, resection may be the best procedure. On the other hand, in some patients whose disease at the time when treatment is started is predominantly in an early pneumonic phase, resolution may proceed without the development of cavities. In such cases long-continued antibacterial treatment and rest may be all that is required. In some of them, encapsulated caseous foci may be left. In patients in whom such residual caseous foci are large, as in those in whom the disease, when first detected, consists predominantly of large caseous foci of considerable size, resection of the affected part of the lung, under cover of antibacterial treatment, must be considered.

Decision about this will depend upon careful appraisal of the localization of the disease by radiography, including tomography, and upon assessment by the physician of the liability to breakdown, taking into consideration the circumstances of the individual patient. Active bronchial tuberculosis requires, in the first instance, antibacterial treatment; but here again the progress of the disease must be assessed clinically, radiologically, and by bronchoscopic inspection, in order to decide whether additional surgical treatment will be required, as will generally be the case when bronchial stenosis develops ; and, if so, at what stage this treatment can be carried out safely and with the greatest economy of time.

It will be clear from the foregoing discussion that the duration of antibacterial treatment will vary greatly according to the objective of treatment in the individual case, and whether or no it is being combined with some other form of treatment. It is probably wise, in any case in which sole reliance is being placed upon antibacterial treatment, to continue it for at least eight, and preferably twelve, weeks after all evidences—clinical, bacteriological and radiological—of activity of disease have disappeared; and some physicians would continue even longer. Similar advice probably applies to patients for whom surgical treatment has been carried out successfully, namely, that antibacterial treatment should be continued for eight weeks after the operation; but here the circumstances of the individual case are so variable that no general rule should be laid down.

In patients with more chronic and extensive disease for which neither collapse therapy nor resection is feasible, the problem of the use of antibacterial drugs is difficult. On the one hand most of these patients will derive benefit from them, and there is now considerable experience of patients of this type who have received very prolonged treatment with antibacterial drugs with very impressive results. On the other hand, the risk of the emergence of resistant strains is high in these patients, and they form a very important potential source of infection to the community. Each case of this sort must be judged individually.

The problems of primary tuberculosis are considered elsewhere in this Bulletin (p. 125) by Professor J. Crofton. In general, caseous lymphadenitis responds poorly to antibacterial treatment, and since many of the manifestations of primary tuberculosis in the lungs are due directly or indirectly to caseous lymph nodes, they would not be expected to respond well to antibacterial treatment. On the other hand, if primary tuberculosis becomes complicated by frank tuberculous pneumonia, the usual response to treatment by antibacterial drugs can be expected.

6. Summary

The present position with regard to the clinical application of antibacterial drugs in pulmonary tuberculosis is reviewed. It is well established that if any of the three most effective drugs at present available—streptomycin, *p*-aminosalicylic acid or isoniazid—is given alone, resistant strains of tubercle bacilli emerge, usually within three months. The rate of emergence of such strains can be diminished greatly by the concurrent administration of any two of these drugs in appropriate dosage. Although current practice is still changing, and is likely to continue to change as a result of fresh basic knowledge, the principle that these drugs should be administered in pairs in order to minimize the rate of emergence of resistant bacilli seems established beyond doubt. The merits of the various available combinations of drugs are briefly discussed. The importance of the integration of antibacterial treatment with other methods, such as collapse therapy and resection, is emphasized.

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THE DIAGNOSIS OF TUBERCULOUS MENINGITIS

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- *b* Onset of the illness
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Before the advent of effective chemotherapy the early diagnosis of tuberculous meningitis was a matter of little importance. In difficult cases it was sufficient to exclude a remediable condition—such as brain abscess—and then to wait, when " any doubt about the diagnosis is soon resolved by the course " (Ford, 1944). Now, however, that we possess efficient and specific remedies such an attitude is inexcusable. Moreover, it is established that, given adequate treatment, the overriding factor in the prognosis of tuberculous meningitis is the stage the disease has reached at the time when treatment is begun (Lorber, 1954). Not only, therefore, must an accurate diagnosis be made but it must be made at the earliest possible moment; and in doubtful cases to withhold treatment until the full clinical and cerebrospinal fluid (c.s.f.) pictures have developed is often to wait too long.

The classical picture of tuberculous meningitis has been so often and so brilliantly described that it is unnecessary to elaborate it further (Whytt, 1768; Trousseau, 1868; Osler, 1892; Gowers, 1893; Barlow, 1899; Still, 1909). When the patient is a child or adolescent who is known to have been in contact with tuberculosis; when the onset of the illness is insidious and accompanied by headache, fever, changes in personality, and increasing lethargy and irritability; when focal neurological signs appear, such as a squint or a hemiparesis; when the Mantoux test is positive and lumbar puncture yields a fluid under increased pressure and showing the typical changes: then diagnosis is easy and is confirmed by the identification of *Mycobacterium tuberculosis* in the c.s.f. or by finding either radiological or ophthalmoscopic evidence of miliary tuberculosis. But both the clinical picture and the c.s.f. findings are open to wide variations (Smith & Daniel, 1947), especially during the early stages of the illness. Since it is these variations that make for difficulty in diagnosis and consequent delay in the initiation of treatment, they will be described here in some detail together with certain other points of diagnostic importance.

1. Clinical Findings

a. Age Incidence

Because tuberculous meningitis is commonest in childhood and adolescence the fact that it can also affect adults is often neglected. Table I shows the age distribution in 160 consecutive unselected cases of tuberculous meningitis treated at the Oxford United Hospitals and at the Military Hospital for Head Injuries, Wheatley, Oxon, together with the survival rate and the number of " late " cases in each age-group. By " late " cases are meant those in which the patients were virtually or completely comatose when treatment was begun, and in which the prognosis is notoriously bad (Medical Research Council, 1948).

TABLE I. AGE DISTRIBUTION IN 160 CONSECUTIVE UNSELECTED CASES OF TUBERCULOUS MENINGITIS

Age (years)	Under 3	3–14	15–20	21–40	Over 40	Total
Total number of cases	31	32	49	33	15	160
Number of "late" cases*	13	12	13	7	8	53
Number of survivors	14	21	30	23	4	92
Percentage surviving	45	66	61	70	24	57.5

* A " late " case is one in which the patient was comatose when treatment was begun.

The large number of patients aged between 15 and 20 is probably due to the inclusion in this series of Service men as well as civilians. Even so, more than a quarter of the patients were over 20 years of age, while no less than 15 were over 40 years of age. The fact that half these latter were already in coma when treatment was begun reflects a common reluctance to diagnose tuberculous meningitis in middle-aged or elderly people.

b. Onset of the Illness

The typical onset, in which vague ill-health continues from about 10 days to three weeks before it is apparent that there is anything seriously wrong, can be modified in either of two ways: the onset may be acute, even abrupt, or the prodromal phase may be prolonged for many weeks. It is the unusually short history that is, perhaps, particularly confusing, especially as the initial cell counts in the c.s.f. tend to be misleadingly high. These points are illustrated by the following case.

Case 1. J.C. 132344. A girl of 18 was sitting by the fire one evening, apparently in her normal health, when she abruptly developed a severe headache and photophobia. That night she slept badly and during the next day the intensity of the headache increased, the pain spread down her neck, and she began to vomit. Thirty-six hours after the onset of the headache she was admitted to hospital.

On admission she was complaining of headache and of intense malaise. She was flushed and feverish but, although a little drowsy, was lucid. Her neck was stiff but there were no other abnormal neurological signs. No evidence of systemic tuberculosis was ever discovered and the Mantoux test was negative to Old Tuberculin (OT) in a dilution of

1/100. Clinically, therefore, the diagnosis appeared to lie between purulent meningitis and subarachnoid haemorrhage.

Lumbar puncture yielded a fluid under greatly increased pressure—containing 469 white cells/mm.^{3}, 72% of which were lymphocytes. The protein was 105 mg./100 ml., the chlorides were 690 mg./100 ml. and the sugar content was diminished. Six days later the c.s.f. contained 3,200 white blood cells, 88% of which were lymphocytes. No organisms were seen on examination of gram-stained films but the Ziehl-Neelsen stain revealed numerous acid-fast bacilli on three successive days.

Treatment was begun immediately with intramuscular and intrathecal injections of streptomycin and the patient made an uninterrupted recovery.

The history of acute onset, together with the large number of lymphocytes present in the c.s.f., makes a diagnosis of benign lymphocytic chorio-meningitis extremely tempting. More confusing still, in these cases a spontaneous, though temporary, remission of symptoms towards the end of the first week of the illness is quite common. This naturally lends strong support to the conclusion that specific chemotherapy is not required and the true nature of the meningitis may be appreciated only when, during the third or fourth week, gross neurological signs appear or the patient goes into a coma. It is interesting to recall that Trousseau himself described these spontaneous remissions and emphasized how misleading they could be (Trousseau, 1868).

At the other end of the scale is the patient who, in spite of some degree of malaise and headache, remains ambulant for weeks. Thus one patient in the Oxford series actually walked up to the medical out-patient department carrying a letter from his doctor suggesting a diagnosis of tuberculous meningitis; while another, who had been ill for nearly two months, sought medical aid only when the intensity of the headache made it impossible for her to bicycle to work. Of particular importance are those patients who develop meningitis while under treatment for miliary tuberculosis. When treated with streptomycin, either alone or in combination with *p*-aminosalicylic acid, probably about one-third of patients with miliary tuberculosis will develop meningitis. In such cases the early symptoms of meningitis may be either masked by the chemotherapy or attributed to the established miliary disease and the meningitis may pass unnoticed until it reaches its terminal stages. All such patients should therefore have a lumbar puncture at least once a week and even minimal changes in the c.s.f. must be regarded with grave suspicion.

The place of isonicotinic acid hydrazide (isoniazid) in the treatment of tuberculous meningitis has not yet been fully evaluated. It appears, however, that the addition of isoniazid to the chemotherapy of miliary tuberculosis greatly diminishes the incidence of meningitis. Nevertheless, routine lumbar punctures should still be performed at frequent intervals.

c. Clinical Picture

In the earliest stages of tuberculous meningitis the clinical picture is simply one of mild meningeal irritation. If there is no history of contact, nor any evidence of past or present systemic tuberculosis, then there is nothing to distinguish the picture from that of any other variety of mild meningitis. In very small children, indeed, the very fact that they have meningitis at all may be overlooked unless it is remembered that, in infants, stiffness of the neck is late and inconstant (Smith & Daniel, 1947) and that the cardinal sign of meningitis is some degree of fullness of the fontanelle (Smith, 1951).

As the illness develops, so the mentality becomes clouded and disturbed. These mental changes are highly characteristic of tuberculous meningitis. Even at a comparatively early stage of the illness the patient becomes drowsy and, a little later, loses his memory for recent events. When undisturbed he sleeps heavily; when roused he may appear fully conscious but has no knowledge of his whereabouts, of the time of day or even of the time of year, and denies ever having seen his doctors or nurses before. If pressed he will begin to fabricate, calling his attendants by the names of past acquaintances and giving a fictitious account of how he comes to be in hospital if, indeed, he recognizes that he is in hospital at all. As soon as he is left alone he turns over in bed and goes to sleep again. As these mental changes develop, so he becomes incontinent of both urine and faeces.

Except in the earliest stages of the disease focal neurological signs are the rule. The commonest is a unilateral or a bilateral external rectus paralysis, or some degree of third cranial nerve palsy. Some degree of hemiparesis is also extremely common. In some cases the knee jerks are diminished or lost while the ankle jerks are retained.

The combination of meningism, mental confusion, and a squint or hemiparesis is so typical of tuberculous meningitis that it can hardly fail to be recognized. It must, however, be emphasized once again that if, for any reason, treatment is not begun until this picture has appeared, then the patient's chance of recovery has already been prejudiced. Table II shows the results obtained in Oxford between December 1949 and July 1952 in patients who were fully conscious and rational and without neurological signs, compared with the results in patients showing the typical clinical picture but not yet in coma when their treatment was begun. Not only does the latter group have the worse prognosis but it is, unhappily, considerably the larger.

TABLE II. RESULTS OF TREATMENT IN PATIENTS WHO WERE LUCID AND WITHOUT FOCAL NEUROLOGICAL SIGNS AND IN THOSE WHO WERE MENTALLY CONFUSED OR SHOWING FOCAL NEUROLOGICAL SIGNS WHEN TREATMENT WAS BEGUN

	Lucid, no focal signs	Mental confusion and/or focal signs	Total
Number of cases	21	33	54
Number of survivors	21	22	43
Percentage surviving	100	66.6	79.6

d. Concomitant Systemic Disease

The demonstration of miliary tuberculosis in a case of non-purulent meningitis makes it virtually certain that the meningitis is tuberculous. In every case, therefore, the chest must be *x* rayed and the fundi oculi searched for choroidal tubercles. The latter are often overlooked because the eyes are not examined sufficiently thoroughly. The pupils should be dilated and the ophthalmoscope focused on the optic disc. A single leash of vessels should be deliberately chosen and followed carefully as far as possible into the periphery. A second leash should then be chosen and again followed from optic disc to extreme periphery. This method greatly increases the chances

of finding any choroidal tubercle that may be present, as tubercles are commonly situated beside or astride a blood vessel.

In young adults or adolescents a recent history of erythema nodosum or of pleural effusion lends strong support to the diagnosis, as does the demonstration of a pulmonary apical lesion or of bone or joint tuberculosis. In children a primary lung complex is the commonest systemic lesion but this may already be well calcified by the time the meningitis develops. In adults the meningitis is usually secondary to chronic fibrocaseous pulmonary tuberculosis but the possibility of a silent tuberculous epididymitis must be remembered. But, common as it is for tuberculous meningitis to be accompanied by signs of past or present systemic tuberculosis, the association is by no means invariable: in many cases no evidence of systemic disease is ever found; and, conversely, the demonstration of systemic tuberculosis—other than a miliary spread—is no proof that the meningitis is tuberculous. For example, we have seen cases of neurosyphilis, of brain abscess and of mumps meningo-encephalitis in patients with strong histories of pulmonary tuberculosis. Most puzzling of all, a child was admitted to the Oxford United Hospitals with mild non-purulent meningitis during a recent epidemic of Bornholm disease (Davies & Warin, 1951, 1953) who, four years before, had been successfully treated by us for proved tuberculous meningitis (Smith, Vollum & Cairns, 1948, Case 7). As he made a rapid and complete recovery without any specific treatment whatever we concluded that this second attack of meningitis was a manifestation of the prevalent virus infection and was not tuberculous.

Apart from the question of systemic tuberculosis, a history of some intercurrent infection such as measles, whooping-cough, otitis media or streptococcal sore throat just before the onset of the meningitis has been found frequently enough to suggest that the relationship is more than fortuitous. It seems reasonable to suppose that these patients were struggling with a latent tuberculous infection and that the intercurrent infection was enough to tip the scales against them. Certainly the story of a child who, after an attack of measles, never seems to make a proper recovery should be regarded with grave suspicion. This point is of importance in the differential diagnosis from brain abscess.

2. Special Investigations

The importance of early lumbar puncture and of full examination of the c.s.f. cannot be exaggerated. No one will claim that lumbar puncture is entirely free from dangers (*Lancet*, 1953), but they are as nothing compared with the risk of allowing a patient to pass untreated into the irreversible stage of tuberculous meningitis for lack of a proper diagnosis.

a. Cerebrospinal Fluid Findings

The typical changes in the c.s.f. are well recognized (Merritt & Fremont-Smith, 1935, 1937; Clark, 1935; Smith & Daniel, 1947; Lincoln, 1947). The pressure is raised and to the naked eye the fluid is colourless and almost clear, though a fine cobweb clot appears in it on standing. There is a moderate pleocytosis (60–400 cells/mm.^{3}) with a preponderance of lymphocytes, the protein content is raised (80–400 mg./ml.) and the sugar and chloride are diminished.

Once again deviations from these typical findings are most often seen during the early stages of the illness. The unusually high cell counts associated with an acute or subacute onset and with a tendency to spontaneous remission have already been described. Another aberration seen in the early days is a normal sugar content. This can be very puzzling in the differential diagnosis from virus infections. The fall in chlorides is much less helpful than the fall in sugar as it takes place late in the illness (Smith & Daniel, 1947).

There is a greater tendency to albumino-cytological dissociation in tuberculous meningitis than in virus infections of the meninges, and a true Froin's syndrome is not very uncommon in advanced cases. Occasionally patients are admitted with a complete spinal block already present and a protein content in the c.s.f. of over 1 g./100 ml. A considerable rise in the protein content of ventricular fluid (80–240 mg./100 ml.) is not uncommon in tuberculous meningitis and when present is a useful point in differentiation from virus infections.

But the cardinal finding, and the one on which the diagnosis must finally rest, is the demonstration of *Myco. tuberculosis* in the c.s.f.

b. Bacteriology

Myco. tuberculosis may be demonstrated by direct microscopy, by culture, or by guinea-pig inoculation. It is essential to establish the diagnosis as soon as possible, and this can usually be done by careful microscopical examination.

i. *Direct examination.* The c.s.f. is centrifuged for 30 minutes at about 3,000 rev./min. The supernatant fluid is pipetted off into a sterile tube. The deposit is carefully removed with a Pasteur pipette, and a drop of this is placed on a clean slide and dried carefully. The dried drop should cover an area about 5 mm. in diameter. The dried film is fixed by heat, stained by Ziehl-Neelsen in the usual way, but counterstained with picric acid. The film is systematically examined with the aid of a mechanical stage.

If sufficient fluid is available, about 2 ml. may be incubated at 37° C. for three or four days. If the organism is not found microscopically in the portion examined immediately, it may often be found in the second portion after incubation, using the same technique.

ii. *Culture.* The remainder of the deposit, which may be mixed with the supernatant fluid of untreated cases, is used as inoculum for culture media. When treatment is started, there may be sufficient antibiotic in the supernatant fluid to inhibit growth. In these cases, only the deposit is used for culture. The initial specimens are usually cultured on Löwenstein-Jensen medium, on Dorset egg medium, and in a modified Kirschner's synthetic medium to which penicillin has been added (Vollum, 1952). Subsequent routine daily specimens are cultured only in Kirschner's medium. The streptomycin in the small amount of deposit used for inoculum may be inactivated by a loopful of sterile active charcoal, but this procedure is usually unnecessary. If viable organisms are present, cultures in Kirschner's medium are usually positive in 14 to 21 days, but cultures are incubated for at least eight weeks before being rejected as negative.

The sensitivity of the organisms to streptomycin or other drugs may be tested by any of the usual techniques (Vollum, 1952). In our experience organisms isolated from the c.s.f. at the beginning of the disease have invariably been sensitive to streptomycin. Organisms isolated from the c.s.f. at a late stage in the disease, or at post-mortem examination, have occasion-

ally shown some increase in resistance, but, with two exceptions, the sensitivity has still been within the therapeutic range. Organisms isolated from the lungs at the same time are frequently more resistant.

iii. *Guinea-pig inoculation.* As much of the original c.s.f. sample as is available, or the remainder of the deposit after centrifugation, microscopy, and culture, is injected subcutaneously into the thigh of a guinea-pig. The animal is killed when it becomes tuberculin-sensitive—or after three months if it remains tuberculin-negative. The organism is isolated from the lesions by the usual technique if it has not previously been obtained by direct culture.

iv. *Typing.* The culture is typed by the usual methods of culture and animal inoculation. In our experience, the bovine type has been rarely found, even in children. The vast majority of the strains are of the human type.

c. Other Investigations

The importance of radiography of the chest has already been discussed. Other investigations should include radiography of the skull, gastric lavage or examination of the sputum, a Mantoux test, a full blood count, and, in selected cases, ventricular estimation or ventriculography. Study of the partition of bromide between blood and c.s.f. is also proving a useful diagnostic measure (Taylor, Smith & Hunter, 1954).

Radiography of the skull often provides some evidence as to how long the increase in intracranial pressure has been maintained. In children some degree of separation of the sutures is common in tuberculous meningitis but is not seen in the virus infections. On the other hand, evidence of long-standing increase in intracranial pressure, such as erosion of the posterior clinoid processes, is hardly compatible with a diagnosis of tuberculous meningitis.

A polymorphonuclear leucocytosis in the blood is quite common—counts of between 14,000 and 23,000 are at least as much in favour of tuberculous meningitis as of brain abscess.

i. *The Mantoux test.* It is often taught that, in children at least, a negative Mantoux test virtually excludes the diagnosis of tuberculous meningitis. This is not our experience. Out of a series of 63 cases the Mantoux test was negative to OT in a dilution of 1/100 on admission to hospital in 14 (i.e. 22%), while a high degree of sensitivity was exceptional (Taylor, Smith & Vollum, 1953). While, therefore, a positive Mantoux test of moderate severity lends support to the diagnosis, a negative test by no means excludes it. The patch test has no place in the diagnosis of this disease.

ii. *Ventricular estimation and ventriculography.* Bilateral ventricular puncture and ventricular estimation can be invaluable in distinguishing between tuberculous meningitis and brain abscess (Cairns, 1949). It has the added advantage of making ventricular fluid available for examination. Quite frequently we have recovered tubercle bacilli from the ventricular fluid when the lumbar c.s.f. has been persistently sterile. If necessary, ventricular estimation can be followed by ventriculography. The characteristic findings in ventriculography depend on the deposition of tuberculous exudate in the cisternae interpeduncularis et ambiens. There are a moderate symmetrical dilatation of the ventricular system (which in itself excludes the presence of a cerebral abscess); a bubble of air held up in the basal cistern just behind the posterior clinoid process; and no air anterior to this or lying over the cortex. How useful this procedure can be is shown by the following case.

> *Case 2. V.T. 167224.* A girl of 4½ years had no relevant past history and no history of contact with tuberculosis. Six weeks before admission she had pushed a sweet up her left nostril. Thereafter she had passed small clots of blood from her nose and had seemed rather unwell. Four weeks later she began to complain of pain in the left ear and became feverish. Shortly after she began to vomit and six days before admission she grew drowsy and unwilling to sit up or talk.
>
> On admission she was still complaining of left-sided earache and was irritable, drowsy and feverish. There was a low-grade papilloedema, her neck was stiff, and the pharynx, tonsils and left ear-drum were injected. There were no other abnormal physical signs. *x* Ray of chest showed changes compatible with a primary lung complex. The Mantoux test gave an equivocal response to OT in a dilution of 1/100. *x* Ray of skull showed an early separation of the sutures. Lumbar puncture yielded a fluid containing 79 cells/mm.³, 20 of which were polymorphonuclear leucocytes; 56 mg. of protein/100 ml.; while the sugar and chloride were normal.
>
> The diagnosis thus rested between brain abscess and tuberculous meningitis. In favour of the former were the history of left-sided otitis following the introduction of a foreign body into the left nostril, the c.s.f. findings which were typical of those of brain abscess, and the negative Mantoux test. In favour of the latter were the radiological changes in the chest. The length of history, the signs of raised intracranial pressure, and, indeed, the otitis itself were compatible with either diagnosis.
>
> In order to exclude the presence of a brain abscess ventricular estimation followed by ventriculography was performed as an emergency measure. The lateral ventricles proved to be capacious and symmetrically placed and the intraventricular pressure was 300 mm. of water. Ventriculography showed that the ventricular system was slightly enlarged; no air had passed up over the cortex but there was a bubble held up in the basal cistern just behind the attachment of the tentorium (fig. 1). The findings were thus typical of tuberculous meningitis and the diagnosis was later confirmed by isolation of *Myco. tuberculosis* from both ventricular and lumbar c.s.f.
>
> The child was treated with intramuscular and intrathecal injections of streptomycin and intrathecal tuberculin (Smith & Vollum, 1950; Smith, 1953), and made a rapid and complete recovery.

iii. *The bromide test.* Recent studies have shown that in tuberculous meningitis the blood c.s.f. barrier to bromide is more frequently and more profoundly modified than in other varieties of non-purulent meningitis. This finding promises to provide the basis for a useful diagnostic test (Hunter, 1953; Hunter, Smith & Taylor, 1954; Taylor *et al.* 1954).

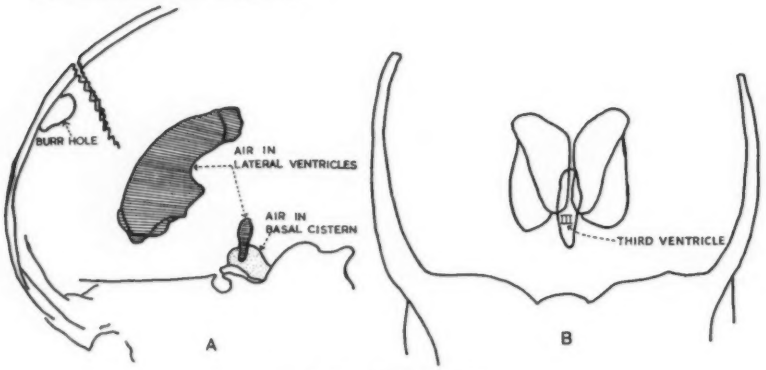
3. Differential Diagnosis

Tuberculous meningitis must be differentiated from any other condition, other than frank purulent meningitis, causing a pleocytosis and elevation of the protein in the c.s.f. The most important of these may be listed as: brain abscess and tumour; virus infections of the central nervous system; spirochaetal infections; and "lymphocytic" meningitis of unknown aetiology.

a. Brain Abscess and Tumour

Brain abscess is put first, not because it is the commonest source of confusion but because it is the condition most certain to lead to disaster if not diagnosed. It should be remembered that whereas intense headache and stiffness of the neck are compatible with early phases of meningitis, they herald the terminal stage of brain abscess. Rapid differentiation is therefore a most urgent matter. When serious doubt

FIG. 1. TRACINGS OF LATERAL AND AXIAL VENTRICULOGRAMS, TAKEN IN THE BROW UPWARDS POSITION, OF A CHILD WITH TUBERCULOUS MENINGITIS (case 2)



A: lateral ventriculogram
B: axial ventriculogram

In the lateral view, a small bubble of air is seen in the temporal horn of the lateral ventricle overlying a larger bubble lying in the basal cistern immediately behind the posterior clinoid processes, i.e., the attachment of the tentorium. No air is seen in front of this. Note also the early spreading of the coronal suture.
The moderate degree of ventricular enlargement is best seen in the axial view.

exists immediate recourse must be had to such special methods of diagnosis as ventricular estimation, ventriculography, or cerebral angiography.

Brain tumours should not cause confusion except when the tumour involves the meninges as in oligodendrogliomatosis, medulloblastoma with spinal metastasis, and carcinomatosis of the meninges. This last is sometimes a cause of confusion in elderly patients. Mistakes will, however, be avoided if it is remembered that tuberculous meningitis can occur, and is treatable, at any age.

b. Virus Infections

The most important member of this group is pre- or non-paralytic poliomyelitis. In the absence of the characteristic lower motor neurone paralysis, differentiation may be extremely difficult. One useful distinguishing point is the mental state: in poliomyelitis the patient often shows intense meningism but remains not only lucid and alert but anxious and apprehensive. In tuberculous meningitis, on the other hand, the patient showing a comparable degree of meningism is usually already drowsy; his awareness of his surroundings is blunted and often his memory is becoming clouded.

Other conditions included in this group are mumps, glandular fever, benign lymphocytic chorio-meningitis, and "lymphocytic" meningitis of undetermined aetiology. The bromide test promises to be extremely useful in this group of cases.

c. Spirochaetal Infections

The commonest causes of confusion in this group are neurosyphilis and non-icteric Weil's disease. Once again the mental state can be a useful distinguishing point between tuberculous meningitis and neurosyphilis, as the modified Korsakoff's syndrome so characteristic of tuberculous meningitis contrasts strongly with the mental changes commonly seen in, for example, general paresis.

Weil's disease will be diagnosed without difficulty if the significance of the albuminuria, the raised blood urea, and the marked leucocytosis in the peripheral blood is appreciated.

In this group diagnosis can in the end usually be established by serological reactions. If serious doubt exists, streptomycin should be given while one awaits the results of the specific tests.

4. Conclusions

Even when every effort has been made there remain a few cases in which a definite diagnosis cannot immediately be established. In such cases full chemotherapy as in a proved case of tuberculous meningitis should be begun immediately, when the subsequent course of the illness will usually resolve any doubts as to the nature of the disease. In the first place, *Myco. tuberculosis* may well be isolated by culture or by guinea-pig inoculation even though never found by direct examination. Secondly, patients with tuberculous meningitis usually lose weight during the first weeks of treatment and remain obviously unwell even though they ultimately recover. In non-paralytic poliomyelitis and in "lymphocytic" meningitis of unknown aetiology, on the other hand, patients improve so rapidly that by the end of about four weeks it is patently absurd to keep them in hospital any longer. Finally, it is sometimes said that once intrathecal medication is begun the c.s.f. picture is so disturbed that treatment must be continued indefinitely for lack of differential diagnosis. This is not our experience: on the contrary, the behaviour of the c.s.f. under treatment has proved of great diagnostic value. A rising protein curve and the appearance of spontaneous fluctuations in the cell counts (Smith, 1952, fig. 2) is highly suggestive, if not pathognomonic, of tuberculous meningitis (Smith & Vollum, 1950; Cairns, Smith & Vollum, 1950; Cairns & Smith, 1952). In any case, it is far better to treat someone unnecessarily for several weeks, when all he will suffer is the discomfort of the injections, than to allow a patient to forfeit his chance of recovery, as happens all too easily if he is, in fact, suffering from tuberculous meningitis.

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A SURGEON LOOKS AT PULMONARY TUBERCULOSIS

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1 Elimination or permanent arrest of the disease
2 Low mortality and morbidity
3 Preservation of maximum function
4 Avoidance of deformity
5 Primary tuberculosis
References

There is an infinite range of reaction of the body to infection with tubercle bacilli, depending upon the number and virulence of the bacilli on the one hand, and the immunity of the patient on the other. Each case of tuberculosis is an individual problem, and surgical intervention must be related to the natural course of the disease, and timed so that it is executed when it is most likely to succeed.

It is useful to divide tuberculous lesions of the lung into those which are reversible and those which are not. Medlar (1950) distinguished caseous pneumonic lesions that cannot heal by natural processes from non-caseous pneumonic ones that can heal by resolution or replacement fibrosis as the result of rest, chemotherapy, or collapse treatment. Caseous foci, together with mechanical complications such as cavitation, bronchostenosis or bronchiectasis, are irreversible, while non-caseous bronchopneumonic ones are reversible. Caseous lesions will probably heal by natural processes only if microscopical in size.

It is the role of the surgeon to eradicate or control irreversible lesions, but maximal healing of reversible foci must be achieved first, by measures such as rest, posture and chemotherapy, while after surgery prolonged medical treatment and observation is essential to ensure that no reactivation occurs. This is why the close collaboration of physician and surgeon is so important and why the surgeon should be asked to intervene at the correct time.

Because of the unpredictable course of pulmonary tuberculosis, and the long period required to assess results, there is difference of opinion about treatment, and the views stated here are personal. The surgeon should embark upon treatment with four aims in view, namely:

i. Elimination or permanent arrest of the disease.
ii. Low mortality and morbidity.
iii. Preservation of maximum function.
iv. Avoidance of deformity.

The first of these is his primary aim, but the others are also important. It is of no help to arrest tuberculosis only to create a respiratory cripple.

The surgeon has the choice of collapse or resection, a choice which may be easy or difficult to make. There are various possible collapse measures. I rely mainly on thoracoplasty with extrafascial apicolysis, which I believe to be the most efficient operation for the closure of tuberculous cavities, but I employ a modified Holst procedure in selected cases. I do not favour plombage, in spite of its several important advantages, because it contravenes the principle that space-filling foreign material should not be left in the body. This is not everybody's view, and Lucas & Cleland (1950) report good results following the use of hollow Perspex and solid Polythene spheres. The choice of operation will be discussed with regard to the four aims of treatment enunciated above.

1. Elimination or Permanent Arrest of the Disease

The irreversible lesions of tuberculosis are largely responsible for continued activity, for preventing natural cure, and for initiating bronchogenic spreads. If these lesions can be eliminated or controlled by surgery there is a good chance that

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reversible lesions elsewhere will remain arrested with the aid of medical treatment. Whatever one may feel about tuberculosis being a generalized disease, there is no doubt that caseous foci and mechanical complications are frequently localized, and often segmental, and it is because of this that surgery has any place in treatment, and that it is likely to be successful. I do not imply that infiltrative disease of a reversible type elsewhere is unimportant, for under adverse conditions activation may occur with the production of further irreversible lesions, and this is why strict medical treatment is so vital both before and after any operation is performed.

The choice between collapse and resection is determined both by the type and by the situation of the disease. Thoracoplasty is successful in the treatment of only one variety of irreversible lesion, namely cavitation, and only if it is situated in the upper lobe or in the apex of the lower lobe. It is not successful in the closure of cavities situated in the middle lobe, the lingula, or the basal segments of the lower lobe. For cavities in these situations, or for caseous, bronchostenotic or bronchiectatic lesions wherever they may be, resection is the only successful type of operation.

There is difference of opinion regarding the efficacy of thoracoplasty in closing cavities in the apex of the lower lobe. In my opinion such cavities can be closed in a high proportion of cases, provided that rib resection and mobilization of the lung are adequate, but resection is usually preferable. If the upper lobe is unaffected, thoracoplasty should not be considered, because it will sacrifice valuable function. If the upper lobe also requires treatment, thoracoplasty is a reasonable procedure and the choice between this and resection, probably supplemented by a small thoracoplasty (ribs 2 to 5) may be a difficult decision. I feel that the latter approach is more likely to secure permanent sputum conversion, with less deformity and more conservation of function.

At the present time the best treatment for cavitary disease of the upper lobe is not decided. This will depend largely upon the mortality and long-term results of resection as compared with thoracoplasty. The exponents of resection must prove that their figures are superior to those of thoracoplasty before the latter well-tried operation is abandoned. I surmise that this will be proved, but even so thoracoplasty will probably still have a place when disease elsewhere, especially on the opposite side, is significant.

Since the aim of the surgeon is to secure permanent arrest of the disease he must leave remaining lung tissue in the best possible position to allow residual reversible lesions, which may or may not be detectable, to remain quiescent. It appears likely that over-distension of lung would be harmful in view of the beneficial effect of relaxation, though this assumption is controversial. Dark & Jewsbury (1953) found that, after both upper and lower lobectomy, ipsilateral reactivation occurred when no measures were taken to prevent over-distension of the remaining lobe, but that this was not so when such measures were employed. However, after pneumonectomy, reactivation did not occur in the opposite lung when no corrective thoracoplasty was performed. Their figures were too small to be conclusive. Bickford, Edwards, Esplen, Gifford, Mair & Thomas (1952) had 10 cases of reactivation in the apex of the lower lobe following upper lobectomy without corrective thoracoplasty, but no case when lobectomy was supplemented by thoracoplasty. Geake & Young (1953) point out that the adverse effect of over-distension may not be as bad as one might expect, because it is more likely to influence normal than diseased lung, owing to their differing distensibilities.

Until this matter is proved, over-distension of remaining lung should be considered dangerous and should not be allowed to occur and, if portions of lung occupying a considerable volume are removed, prompt and permanent measures must be taken to protect the remainder. The safest way of doing this is to perform corrective thoracoplasty. This should be done after the removal of a lung or a bulky lobe, but is probably unnecessary in the case of segments or contracted lobes. Temporary methods of preventing over-distension are theoretically unsound.

2. Low Mortality and Morbidity

The operative (hospital) mortality for thoracoplasty given by various authors differs considerably, as shown in Table I, depending upon such factors as choice of case and availability of effective chemotherapy.

TABLE I. HOSPITAL MORTALITY AND LATE MORTALITY OF THORACOPLASTY

Author	Number of cases	Hospital mortality		Late mortality of patients surviving operative period			
		Number	Percentage	Number traced	Period of observation (years)	Number known to have died	Percentage of deaths in number traced
Holmes Sellors (1947)	633	17	2.7	571	1–10	55	9.6
Price Thomas (1950)	304	29	9.5	243	unstated	15	6.2
Refsum (1951)	391	27	6.9	{all all	5 10	— —	17 33
Keers & Gowar (1953)	251	4	1.6	—	—	—	—

Many of the patients treated by the first three of the above authors were operated upon before streptomycin became available.

Resection can be performed with as low a mortality as thoracoplasty, as the following figures show, but the operation and after-care require more skill and attention. Bickford *et al.* (1952) report 729 resections with 14 postoperative deaths (within three months), a mortality of only 1.92%. There were 178 pneumonectomies, with nine deaths (5.1%); 292 lobectomies or lobectomies plus segmental resections, with four deaths (1.4%); and 259 segmental resections, with one death (0.4%). Two hundred and sixty-six resections were performed on 259 patients admitted to Sully Hospital, Sully, Glamorganshire, under Dillwyn Thomas, with five early deaths (first three months), a mortality of 1.88%. Amongst these there were 118 pneumonectomies with three deaths (2.5%), 81 lobectomies with no death, and 50 segmental resections with one death (2%).

With regard to permanent arrest of the disease, Holmes Sellors (1947) and Price Thomas (1950) report sputum conversion rates for thoracoplasty survivals of 84% and 86% respectively. These figures though good give no ground for

complacency, for they represent a failure rate of about 15%. Furthermore, if the search is diligent, the occasional positive sputum is liable to be found after thoracoplasty, especially when the patient has a cold, and such patients may infect others, especially children, although remaining well themselves.

In Holmes Sellors' series, late deaths occurred in 55 out of the 571 patients who were traced, but 10 of these were known not to be due to tuberculosis. Refsum's figures for late deaths are important, since in his series every case was traced; 33% of those of the patients in his series who survived the operative period were dead after 10 years. Only 62% of his 391 patients became free of symptoms (six consecutive negative sputum smears, cavities closed, no signs of active tuberculosis) and reactivation, usually on the opposite side, subsequently occurred in 20% of these, of whom one-half died.

The above figures indicate that thoracoplasty fails to convert the sputum in about 15% of patients, and that following successful operations reactivation occurs in a proportion, usually on the side of the thoracoplasty in the first year, or on the opposite side at a later date. The results are probably improved by closing cavities and converting the sputum when possible, by the use of bed-rest, posture and streptomycin, before thoracoplasty, and I believe that these means should always be tried.

At present, long-term results following resection are not available. In the series of Bickford *et al.* (1952) there were five late deaths, of which one was not due to tuberculosis (the great majority of the patients were followed up for four years or less, a few up to eight years), and in that of Thompson, Savage & Rosser (1954) there were two late deaths, the follow-up period varying from three months to five years. Of the patients in the latter series, 95% were well and free from all signs of active disease. In the series of Bickford *et al.* (1952) the corresponding figure was 88%.

It is customary in many clinics to choose cases for resection in which the disease is localized or strictly unilateral, while those with more extensive and widespread disease are selected for thoracoplasty. Furthermore, excisional surgery has been practised extensively only since the advent of streptomycin. These two factors favour the figures for resection as compared with thoracoplasty.

3. Preservation of Maximum Function

The preservation of maximum function should always be the surgeon's endeavour, provided that permanent arrest of the disease is not jeopardized. In order to achieve this, a minimum of functioning lung should be removed or put out of action, the chest wall should be kept intact, and the action of the diaphragm should be preserved. All these objectives may not be possible to achieve, but they should always be carefully considered.

We ought to know how much function is reduced by the removal of various amounts of lung, or by the collapse of various amounts of chest wall and lung, but unfortunately our knowledge is still not precise, despite considerable investigation. Resection may improve or diminish function. As Mannix, Gerbasi, O'Brien, Adler, McAlpine & Kerr (1953) remark, improvement may follow the elimination of toxaemia or the removal of bronchial secretions or areas of lung acting as unaerated shunts. On the other hand, function is reduced when healthy lung is removed or when pleural or pulmonary complications occur, or if the remaining lung is allowed to over-distend. Further loss of function will accrue if the chest wall is damaged or the diaphragm is paralysed. Our operative and postoperative treatment must be designed to remove or collapse the least amount of lung consistent with control of the disease, to preserve as far as possible the action of the chest wall and diaphragm, to prevent complications such as bronchopleural fistula, empyema, or pulmonary collapse, and to avoid the development of scoliosis and pulmonary distension. Some of these aims may be mutually antagonistic, for it may be desirable to injure the chest wall by performing a thoracoplasty in order to reduce the risk of bronchopleural fistula, or over-distension of remaining lung.

Over-distension of remaining lung was discussed with regard to its probable adverse effect on residual quiescent lesions, and its influence on function must now be considered. There is difference of opinion in this respect. Overholt, Walker & Etsten (1953) concluded that hyperinflation does not cause pulmonary disability, while Neuhof & Nabatoff (1948) found none of the angiographic changes after pneumonectomy described by Robb & Steinberg (1940) in cases of emphysema, such as dilatation of the main pulmonary arteries and thinning of the peripheral branches. They concluded that distension of the lung is simple in nature and not associated with emphysema. Pacheco & del Castillo (1952), after angiographic studies, believe that lobectomy and pneumonectomy cause a state of respiratory insufficiency in remaining lung tissue that is allowed to over-distend.

Gaensler & Streider (1951) found no preponderance of evidence that chronic over-distension after pneumonectomy leads to true pulmonary emphysema with disruption of lung parenchyma, but they thought that this would probably be the end result. Many of their patients with marked over-distension showed only one manifestation of emphysema, namely, an increased ratio of residual volume to total capacity, and in only a few was there progressive decrease of maximum breathing capacity. Other evidence of emphysema was absent. But elsewhere these authors state that simple over-distension may at an early date develop into true obstructive emphysema (American terminology). Charbon & Adams (1952) showed that after pneumonectomy in dogs the average right ventricular pressure was 28% lower when over-distension was prevented than when it was allowed to occur.

Cournand, Riley, Himmelstein & Austrian (1950) found a close correlation between over-distension and loss of function after pneumonectomy. When over-distension did not occur, or was prevented by thoracoplasty, function was good, whereas when it did develop function was poor, and was not improved in four out of six cases in which a late thoracoplasty was performed for its correction. The paper by these workers gives convincing evidence that from the functional standpoint over-distension should not be permitted, and that means to combat it should be instituted early. Gaensler & Streider (1951) have shown that after pneumonectomy over-distension occurs almost entirely during the third and fourth months, and after lobectomy it must take place very early.

If we believe that over-distension adversely affects both residual tuberculous lesions and function, then early, vigorous and permanent methods should be taken to prevent its occurrence. The safest method at present available is corrective thoracoplasty, and the damage inflicted on the chest wall must be accepted. Although plombage preserves more function and

causes less deformity it is not acceptable to many because of the risk of tuberculous or pyogenic complications which attend it. Thoracoplasty will be necessary after the removal of a lung or an expanded lobe, but probably not after the removal of one or two segments or a collapsed lobe.

Thoracoplasty (not with resection) sacrifices function by collapsing active lung and by damaging the chest wall. Further loss is caused if pleural or pulmonary complications or scoliosis develop. Woodruff, Merkel & Wright (1953) found that, after removal of six ribs or less, function was better than when eight ribs or more were taken. All workers agree that the development of scoliosis seriously affects function. Its development can be minimized by the technique of operation and by competent physiotherapy. Powers & Himmelstein (1951) explain the production of scoliosis by damage inflicted on the muscular support of the thorax. They describe four groups of muscles which act in opposition on the two sides of the chest, namely, the paraspinals, the scalenes, the pectoralis minor, and the serratus anterior. Complete excision of the first two ribs detaches the scalenes, excision of the transverse processes the paraspinals, and removal of long anterior segments of the second, third, and fourth ribs detaches the pectoralis minor. While the scapula is being freed, the upper digitations of serratus anterior are divided. The muscles of the other side are now unopposed and undergo contracture. This must be prevented by physiotherapy until the muscles gain new supports, and the operation should be designed to damage these structures as little as possible.

If it is essential to maintain as much function as possible, the standard type of thoracoplasty may be replaced by a Holst type of operation, or by apicolysis with some form of plombage. I rarely use the latter method, for the reasons already given.

4. Avoidance of Deformity

The surgeon should try to avoid deforming his patients, but this must be subordinate to control of disease and preservation of function. Resections that do not require supplemental thoracoplasty have the great advantage that the patient is not mutilated. This holds for wedge or segmental resection or the removal of collapsed lobes. After the excision of an expanded lobe, over-distension of the remaining lobe can be prevented by the removal of the second, third, fourth and fifth ribs, and this causes very little deformity. When pneumonectomy is supplemented by thoracoplasty, preservation of the first rib will reduce disfigurement.

In the case of thoracoplasty the removal of only five ribs produces little deformity because the scapula does not fall in, but, when seven or more ribs are taken, deformity is greatly increased by this mechanism. Another important cause of disfigurement is impaction of the angle of the scapula on the highest remaining rib, with resulting elevation of the shoulder. This frequently occurs after six ribs are removed, and may do so after seven are removed, if the scapula is large. For tuberculous lesions of small extent confined to the apex of the lung, a five-rib thoracoplasty effectively controls the disease and produces a minimum of deformity and loss of function. For other lesions seven or more ribs require removal, and it is probably wiser to take eight unless the scapula is small. Other points in operative technique have been discussed above. Physiotherapy plays a part of great importance in maintaining a good posture and in preventing scoliosis.

5. Primary Tuberculosis

An important field for surgery is open in consequence of the work of Dillwyn Thomas (1952), who has shown that some cases of primary tuberculosis cause acute or chronic ill-health, or death, despite medical treatment, and that such cases can be treated successfully by surgery.

It is the glandular component of the primary complex which usually causes illness. The glands enlarge, caseate and soften and may compress or rupture into adjacent structures, especially the trachea and the main, lobar or segmental bronchi. Pressure on the trachea may occasion severe dyspnoea, while rupture of a glandular cold abscess into it is often fatal.

Compression of a bronchus may cause obstructive emphysema or collapse of the associated area of lung, and these events may sometimes be observed to occur in sequence. Perforation into a bronchus may lead to spontaneous cure by expectoration of the entire glandular contents, but this cannot be expected, and more often an inhalation tuberculous pneumonia results. Specimens of lung removed in such cases by Dillwyn Thomas, and a few by myself, show caseating or non-caseating tuberculous pneumonia, or a combination of the two conditions. Whether or not caseation occurs probably depends upon the number of viable tubercle bacilli aspirated. Some caseation was demonstrated in a majority of the specimens by Dr R. Seal (personal communication), and in most he found destruction of lung architecture sufficient to make return of function impossible, or unlikely. Bronchography shows complete or partial bronchial obstruction or bronchiectasis.

Intermittent discharge of caseous glands into a bronchus may occur over long periods of time and so maintain infection indefinitely. In most children with lung lesions, gastric washings are found to contain viable tubercle bacilli indicating the presence of active bronchopulmonary tuberculosis, and there is evidence to show that bacilli may continue to be present in the gastric washings for years. With infection so maintained, it is not unreasonable to suppose that the collapsed, bronchiectatic and pneumonic segments of lung may well be a possible source of future adult tuberculosis, occurring either at the same site, or elsewhere in consequence of bronchial aspiration.

With the above in view, the following indications for surgery may be formulated, especially when the patient is acutely ill and not thriving or if tubercle bacilli are present in the gastric washings.

i. Compression of the trachea, causing respiratory distress.

ii. A glandular mass visible on the radiographs, with distortion of a main, lobar or segmental bronchus.

iii. A visible glandular mass with obstructive emphysema.

iv. A persistent pneumonic, lobar or segmental shadow in the lung, with or without a visible glandular mass. It is impossible to distinguish radiologically between collapse, non-caseous tuberculous pneumonia and caseous tuberculous pneumonia.

All will agree with the first of these indications. The second and third indications are put forward with the object of protecting the patient from the consequences of bronchial rupture, and the fourth with the object of removing the glandular mass and the associated area of tuberculous pneumonia.

The great merits of Dillwyn Thomas's work are firstly that it confirms that bronchial perforation is common, and that a high proportion of pulmonary shadows are caused by aspiration tuberculous pneumonia, and secondly that it demonstrates that removal by thoracotomy of glandular masses, and of the lung lesions to which they give rise, can be performed with safety, and with benefit to the patient. I agree wholeheartedly with the views of Dillwyn Thomas and believe that his work should be given serious consideration by all who are interested in tuberculosis. The investigation of primary lesions should be far more thorough than is usually the case.

ACKNOWLEDGEMENT

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LONG-TERM RESULTS OF ARTIFICIAL PNEUMOTHORAX TREATMENT

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1 The Frimley experience
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The discovery of antibacterial agents that attack the tubercle bacillus and that can be used with relative safety is bound to revolutionize the treatment of pulmonary tuberculosis. Already these drugs are being used as a main line of treatment either by themselves or combined with new surgical procedures that have been made practicable by their discovery. As yet we do not know what the outcome of these therapeutic adventures will be, nor can we compare the results of these new methods of treatment with those achieved in the past by other means. Nevertheless, some forms of treatment which were previously popular are already being supplanted by the newer methods, and this gives rise to a real danger that we may discard some valuable therapeutic weapons before they have been proved to be superseded. This applies especially to artificial pneumothorax (AP) which, until a few years ago, was the most widely used treatment for pulmonary tuberculosis, but is now rapidly going out of fashion. Clinicians are particularly ready to discard AP because it has a reputation for being fraught with serious complications and because there has never been any general agreement about the efficiency of this treatment when judged by long-term results.

1. The Frimley Experience

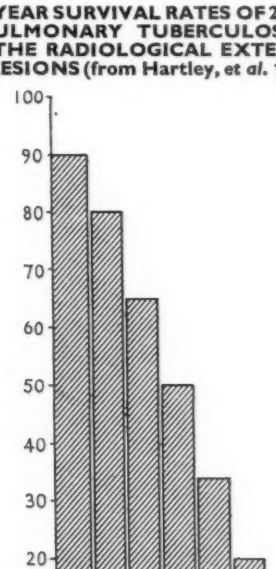
The findings of a follow-up investigation recently completed at the Brompton Hospital Sanatorium, Frimley, are therefore of particular interest at the present time, since they show what can be achieved by AP treatment properly employed, and they provide a yardstick by which to measure the long-term results of newer forms of treatment when these become available.

The investigation was based on the after-histories of 955 patients with cavitated disease discharged from the Sanatorium during the five-year period, 1937 to 1942; this ensured a minimum follow-up of eight years, and only 1.13% were lost from observation. The results were subjected to a thorough statistical analysis and they have been published in full elsewhere (Foster-Carter, Myers, Goddard, Young & Benjamin, 1952); for the purpose of the present article we are only concerned with the fate of 457 patients with cavities who were treated by unilateral AP.

2. Initial Extent of Disease

When groups of patients were compared, every effort was made to ensure that such groups were truly comparable in respect of age, sex, occupation and extent of disease. The latter is particularly important because it was found that the most powerful factor influencing survival was the extent of disease on admission to hospital. This was shown (fig. 1) by Hartley, Wingfield & Burrows (1935), and throughout the whole of this investigation our findings confirmed the general statement that the expectation of survival in pulmonary tuberculosis is inversely proportional to the radiological extent of the initial disease. It follows that any comparison between the fate of two groups of tuberculous patients is valueless unless the extent of disease in the two groups is similar. Failure to appreciate this in the past has accounted for some of the discrepancies between the results of pneumothorax

FIG. 1. FIVE-YEAR SURVIVAL RATES OF 2,759 PATIENTS WITH PULMONARY TUBERCULOSIS, ACCORDING TO THE RADIOLOGICAL EXTENT OF THEIR INITIAL LESIONS (from Hartley, *et al.* 1935)



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Survival rates are shown as percentages.
Number of cases in each group is shown at foot of each column.
Numbers 1, 2, 3, 4, 5, 6 show number of zones affected. (Zones were determined by the drawing of imaginary lines through the second and fourth costal cartilages, on a postero-anterior radiograph.)

treatment described by different authors, which have caused the present uncertainty about the value of this treatment.

3. Radiological Classification

It seemed desirable to express our results in a form which would be roughly comparable with the classifications sponsored by the Ministry of Health in Great Britain and the National Tuberculosis Association of America (NTA) but which would give a more accurate estimate of the extent of disease on admission. Accordingly we adopted three main classes delimited by the number of zones involved. (Zones were determined by the drawing of imaginary lines through the second and fourth costal cartilages, on a postero-anterior radiograph.)

Class I. Patients with not more than one pulmonary zone involved (Ministry of Health classification, group R.1; NTA classification, *Minimal*).

Class II. Patients with unilateral or bilateral disease involving two or three zones (Ministry of Health classification, group R.2; NTA classification, *Moderately Advanced*).

Class III. Patients with bilateral disease involving four or more zones (Ministry of Health classification, group R.3; NTA classification, *Far Advanced*).

4. Selection

It is important to remember that our patients were selected in the sense that all of them had been seen by a physician and considered likely to benefit from treatment. After a period in hospital, they were again reviewed and considered well enough to proceed to the Sanatorium. It is difficult to assess the precise value of these selections, since they depended upon clinical impressions as well as on recorded facts, and it may be argued that they detract from the value of our results. But, on the other hand, most physicians in their hospital practice are dealing with patients who have been selected in just this way, and figures relating the fate of the tuberculous population as a whole are no help to them. This investigation traces the fate of 457 typical tuberculous patients with cavities such as are commonly admitted to hospital for treatment. All of them had unilateral pneumothoraces and none had any antibacterial therapy. The results show, therefore, what can be achieved by AP alone in properly selected cases.

5. Type of Artificial Pneumothorax

The patients were divided into three groups according to the type and efficacy of the collapse obtained. This was judged by the appearance of the pneumothorax on a straight *x*-ray film of the chest, and by the behaviour of the cavity (fig. 2).

i. *Satisfactory Collapse.* This group comprised 92 cases in which the lung appeared to be completely free, either from the start of the pneumothorax or after adhesion section, and the cavity or cavities appeared to close.

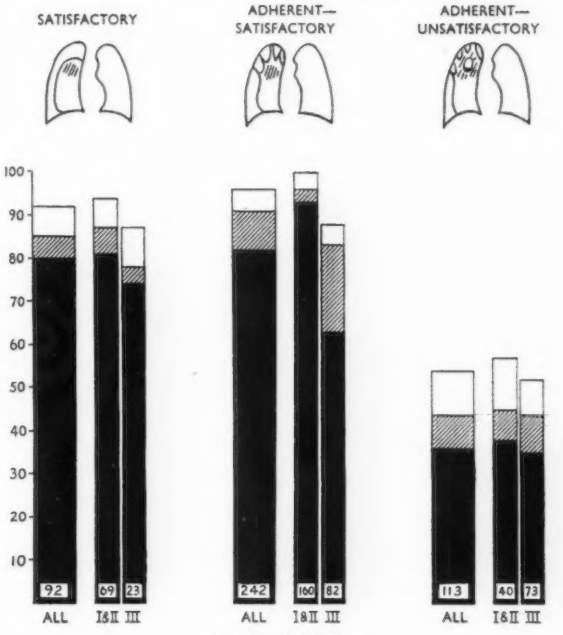
There was a small group of 10 patients whose pneumothoraces appeared anatomically satisfactory but whose cavities did not close; these will be considered separately later.

ii. *Adherent-Satisfactory Collapse.* In these 242 cases there were adhesions over the diseased area which were not divided, but the cavity or cavities appeared to close within a year from the induction of the pneumothorax.

iii. *Adherent-Unsatisfactory Collapse.* This group comprised the remaining 113 patients who also had adhesions over the diseased area but whose cavities did not close and were still visible one year after the induction of the pneumothorax. Patients with unclosed cavities who developed an empyema before the end of a year were also included in this group. The arbitrary limit of a year was adopted because it was felt that after that time the chances of obtaining cavity closure were very small indeed.

It can be seen from fig. 2 that of the 92 patients whose pneumothoraces were classed as *Satisfactory*, 80% survived eight years; of the 242 *Adherent-Satisfactory* patients, 82% survived, but of the 113 *Adherent-Unsatisfactory* patients, only 36% survived the same period.

FIG. 2. SURVIVAL OF PATIENTS GIVEN ARTIFICIAL PNEUMOTHORAX TREATMENT, ACCORDING TO TYPE OF COLLAPSE AND EXTENT OF DISEASE



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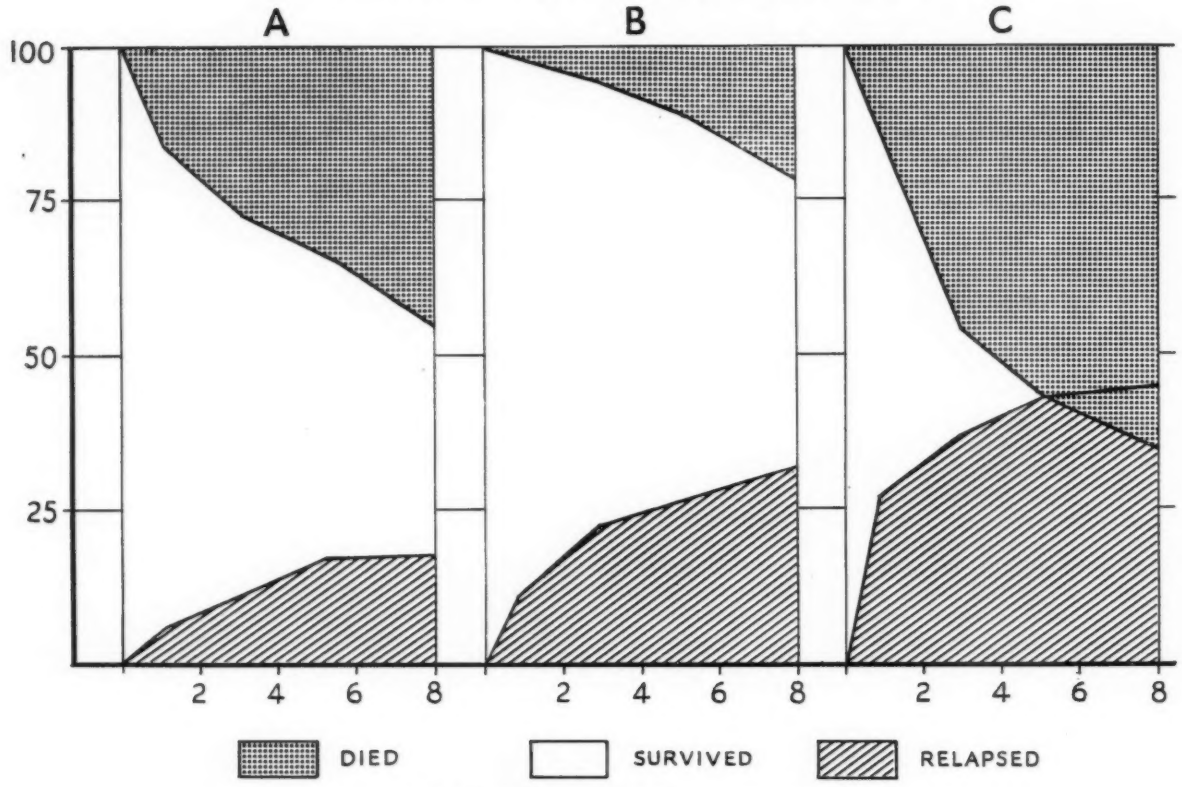
The number at the foot of each column is the number of cases in that group.

Extent of disease is shown in roman numerals:
I: one zone involved
II: two or three zones involved
III: four or more zones involved

Survival rates are shown as percentages:
□ survival for 3 years
▨ survival for 5 years
■ survival for 8 years

FIG. 3. COMPARISON OF RATES OF SURVIVAL AND RELAPSE



A: no collapse therapy (311 cases)
B: effective artificial pneumothorax (332 cases)
C: ineffective artificial pneumothorax (113 cases)

Abscissae: number of years since admission to hospital
Ordinates: survival rates and relapse rates expressed as percentages

6. Extent of Disease

Figure 2 also shows the survival rate of the patients according to the extent of their disease. Most of those in the *Satisfactory* category fell into Classes I and II. Rather more of the *Adherent-Satisfactory* patients had extensive disease, but their survival rate as a whole was slightly better than that of those who had a free lung. In the *Adherent-Unsatisfactory* group no less than 65% of the patients had extensive disease and therefore started with a handicap. The survival rates in this group were worse, not only for the whole group but also for each class.

7. Bacteriology of Sputum

Sputum conversion occurred in 80% of the patients with positive sputum who had a satisfactory collapse, and in no less than 85% of those who had adhesions but whose cavities closed; these *Adherent-Satisfactory* patients also had a slightly better survival rate. In the *Adherent-Unsatisfactory* group of patients, whose cavities were not controlled, the figures were very different. Only 41% had a negative sputum on discharge and of these only 48% survived eight years.

The results so far described show that, provided the cavity closed, the presence of adhesions did not affect the long-term prognosis, nor did it impair the efficiency of the pneumothorax as judged by sputum conversion.

8. Relapse

The next step was to find the incidence of serious relapses in patients having pneumothorax treatment, and we judged this by the percentage of patients who had to be readmitted to hospital at a later date for further collapse therapy. The presence of adhesions was not associated with a higher incidence of relapse: 37% of the patients with free lungs required further treatment, compared with only 30% of those who had adhesions but whose cavities closed.

In fig. 3, all the 332 patients with or without adhesions, whose cavities closed, have been grouped together under "effective AP". They are compared with a similar group of

311 patients who had cavitated disease but had no initial collapse therapy, and also with the 113 pneumothorax patients whose cavities did not close. The incidence of relapse requiring further treatment was higher in the "effective AP" group than in those who had no collapse therapy, but their ultimate survival rate was much better. This is because the high mortality among those who did not have collapse therapy reduced the population at risk and thus accounted for the smaller number requiring further treatment. The relapse rate for patients with pneumothoraces that did not achieve cavity closure was 43%, considerably higher than in the other groups. More than half these patients needed further measures of collapse therapy in an attempt to close the persistent cavity in the originally affected lung. It will also be seen that the prognosis in these patients was worse than that in the patients who had no collapse therapy—a finding which tells its own story.

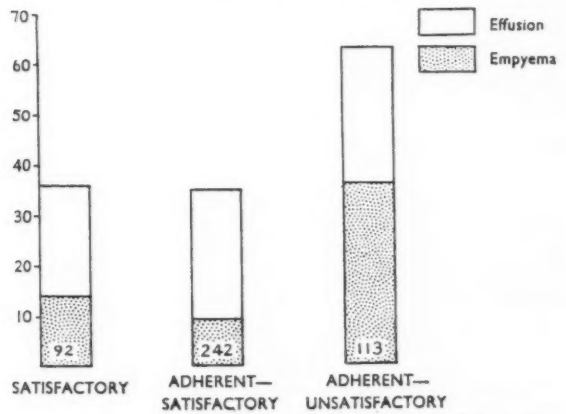
9. Effusion and Empyema

Figure 4 shows the incidence of effusion and of empyema in our series. Transient effusions were ignored; the fluid had to be enough to cover the diaphragm and to be present for more than one month. An empyema was defined as a purulent effusion; a predominance of polymorphs was the diagnostic criterion.

In the *Satisfactory* group, fluid was present in a total of 36%, as compared with 35% in the *Adherent-Satisfactory* group. This shows that, contrary to common belief, the presence of adhesions alone was not associated with an increased incidence of fluid, provided that the cavity closed. But when the adhesions prevented cavity closure, fluid was present in almost twice as many cases (63%) and this appears to be the real danger. This was amply confirmed by the incidence of empyema; there were actually fewer empyemas in the *Adherent-Satisfactory* than in the *Satisfactory* group (9% against 14%), but in the *Adherent-Unsatisfactory* group the incidence was no less than 36%.

Clear effusions, which were found in 26% of all cases, had virtually no effect on the prognosis. Empyema, on the other hand, was a very serious complication and carried a death-rate of 56%.

FIG. 4. INCIDENCE OF PLEURAL FLUID IN PATIENTS GIVEN ARTIFICIAL PNEUMOTHORAX TREATMENT, ACCORDING TO TYPE OF COLLAPSE



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Figures of incidence are expressed as percentages.
Number of cases in each group is shown at foot of each column.

10. Fate of the Pneumothorax

At the end of the period of observation, some patients still had pneumothoraces, while in other cases the treatment had been terminated. The patients were, therefore, divided into two groups: *AP Maintained* and *AP Terminated.* The latter group was split into: *Deliberate Termination* and *Enforced Termination.* Under the heading of *Deliberate Termination* we included only those cases in which the pneumothorax was abandoned because the clinician considered that it had achieved its object: all other cases were classed as *Enforced Termination.*

Figure 5 shows the fate of all the patients according to their various groups. First, those whose pneumothoraces had been maintained until the end of the period of observation or until their death: in the *Satisfactory* group the pneumothorax was maintained in 15 patients (16%) and the crude survival rate was 53%, but three of the seven deaths were not due to tuberculosis. In the *Adherent-Satisfactory* group, 21% of the pneumothoraces were maintained and of these patients 67% survived. In the *Adherent-Unsatisfactory* group, the pneumothorax was maintained in 25%, of whom only 11% survived.

If we turn now to those patients whose pneumothorax treatment was terminated, it is noteworthy that the average period of observation after re-expansion of the lung was approximately five years in all cases; the relevant part of fig. 5 therefore shows the survival rates five years after termination of the pneumothorax.

In the *Satisfactory* group, the pneumothorax was terminated deliberately in 47%, with a 91% survival rate. In 37% there was enforced termination of treatment, before its object was considered to have been achieved: 76% of these survived. At the end of the follow-up 91% of the survivors were well and working.

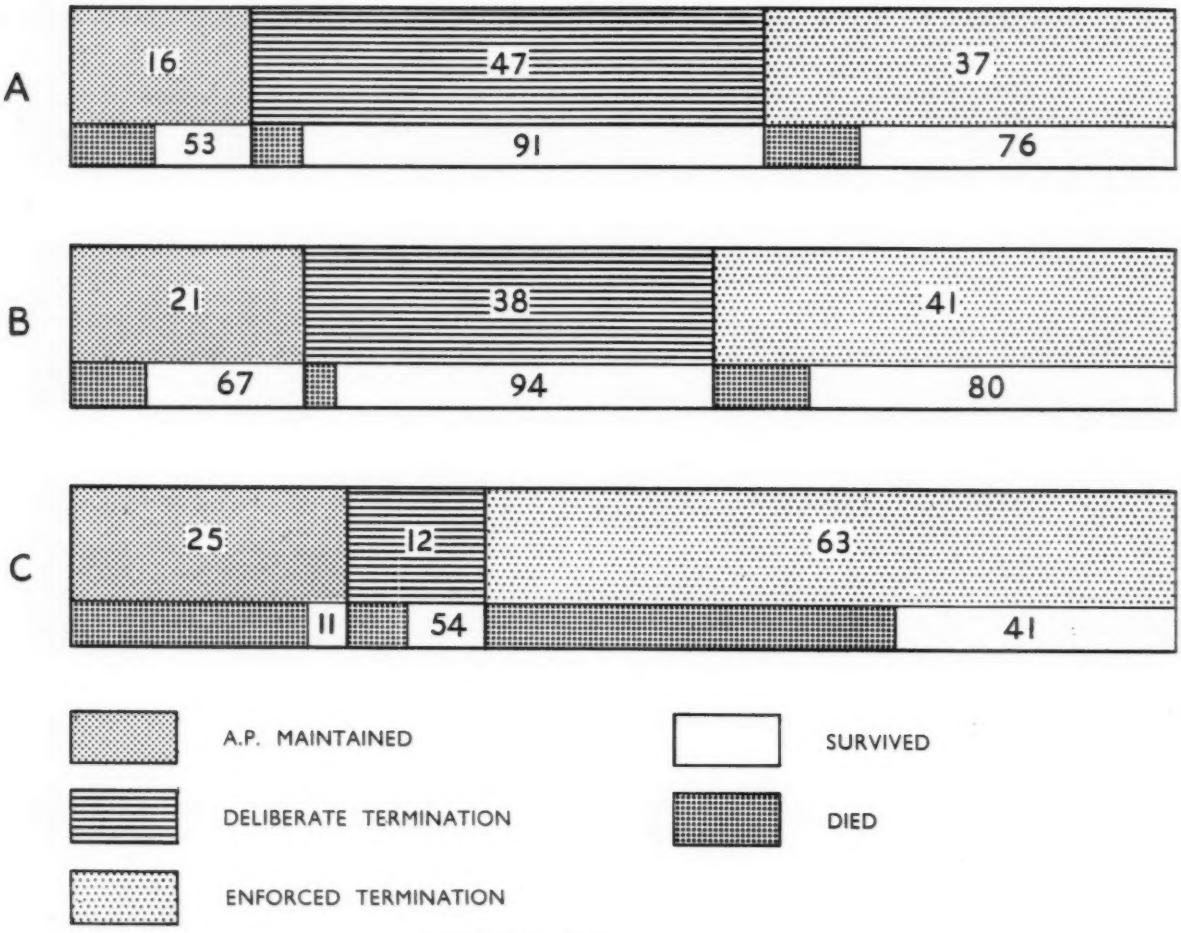
In the *Adherent-Satisfactory* group enforced termination occurred in a rather higher proportion of patients. Nevertheless, the survival rate of those who had enforced termination was 80%, while following deliberate termination it was no less than 94%. Of the survivors 88% were well and working at the end of the observation period.

Finally, in the *Adherent-Unsatisfactory* group the results were, once again, very different. In the majority of patients in this group the pneumothorax treatment had to be given up because of complications. In only 13 patients (12%) was it terminated deliberately and for this group the survival rate five years later was 54%. Enforced termination took place in the remaining 63%, with a corresponding survival rate of 41%. Taking all the 36 survivors, however, no less than 31 were working. This appears to be an example of the survival of the fittest.

11. Extent of Adhesions

Most patients in the *Adherent-Satisfactory* group had multiple adhesions over the diseased area; only 4% had adhesions confined to the superior mediastinum. But the

FIG. 5. PROPORTIONS OF 457 PATIENTS WITH VARIOUS TYPES OF ARTIFICIAL PNEUMOTHORAX, IN WHOM THIS TREATMENT WAS MAINTAINED UNTIL DEATH OR END OF OBSERVATION PERIOD, TERMINATED DELIBERATELY, OR TERMINATED OF NECESSITY, WITH SURVIVAL RATES IN EACH SUB-GROUP



A: *Satisfactory* collapse
B: *Adherent-Satisfactory* collapse
C: *Adherent-Unsatisfactory* collapse
All figures are expressed as percentages.

survival rates and the incidence of pleural complications were found to be the same whether the adhesions were few or many. It must be remembered that cavity closure was achieved by all the pneumothoraces in this group, however inelegant their appearance, and it was evidently a more important factor for success than absence of adhesions.

12. Satisfactory Collapse with a Persistent Cavity

Mention has been made of ten patients who had anatomically satisfactory pneumothoraces complicated by tension cavities that failed to close. In the light of modern knowledge it is clear that the underlying cause was tuberculous bronchitis. Only three of these ten patients survived: nine of them developed pleural complications; three had effusions, and six empyemas. Their fate merely confirms the view, which is now generally accepted, that tension cavities are an absolute contra-indication to the use of pneumothorax.

13. Conclusions

This investigation has shown, first and foremost, that AP alone has achieved excellent results when used rightly. Any treatment that can give an eight-year survival rate of 90% in 230 patients with cavities who had up to three pulmonary zones diseased (" effective AP ", Classes I and II) is

worthy of serious consideration and should not be discarded lightly.

Provided that no obvious contra-indication exists, pneumothorax should still be considered when the treatment of a patient with pulmonary tuberculosis is planned. The chief contra-indications are extensive lung destruction, acute exudative disease, proved tuberculous ulceration of a major bronchus, the presence of tension cavities and of large, solid tuberculous foci in the lung.

Contrary to the accepted view, a pneumothorax which is complicated by adhesions is not necessarily dangerous or ineffective. We have found ample evidence in our series to prove that, if the lung is relaxed sufficiently to allow the cavity to close, the presence of adhesions is of no importance. As in other forms of collapse therapy, cavity closure is the main objective of pneumothorax treatment and, provided that this is achieved, adhesions may safely be left alone.

In patients with acute exudative disease, antibacterial therapy will usually produce rapid resolution and make it safe to collapse the lung within a comparatively short period of time. Indeed the immediate good results of antibacterial treatment are often so dramatic that the physician may be tempted to decide that collapse therapy is not necessary, especially if cavity closure has occurred. Nevertheless, the evidence suggests that, until more is known of the long-term results of antibacterial treatment, it is safer to institute collapse therapy in spite of this initial improvement. It is common knowledge that the disease not infrequently becomes active again and that cavities reopen when the antibacterial treatment is terminated, and it is logical to assume that, as in the past, firm healing will be more likely to occur if the lung is relaxed by a pneumothorax. It is also reasonable to suppose that, if pneumothorax treatment is supplemented with antibacterial drugs, the incidence of complications will be reduced and the ultimate results will probably be even better than those in our series.

Pneumothorax has distinct advantages over resection, which is now commonly employed as an alternative treatment. Tuberculous foci are so often multiple and scattered throughout the lung that general relaxation is more likely to succeed in producing quiescence than local removal of the more heavily diseased areas. Pneumothorax is essentially a temporary and reversible measure and should be used as such: with proper choice of cases the functional results are good and the so-called "frozen lung" is uncommon and rarely causes serious disability. Resection, on the other hand, produces permanent changes in the lung and sometimes has to be combined with a plastic operation on the chest wall. Again, a trial pneumothorax does not prevent the use of resection if this is necessary at a later date, whereas the converse is not true.

Whichever method is employed, the outcome is never entirely predictable, but from the evidence available there is no reason to suppose that the ultimate results of resection, either in arresting the disease or in restoring function, will be superior to those obtained by pneumothorax in suitable, selected cases.

It is, of course, essential that new methods of treatment should be given a thorough trial, under carefully controlled conditions, so that in a few years' time we may be in a position to assess their value. Meanwhile, we should continue to use AP, combined with antibacterial drugs, in the treatment of those cases in which we know from past experience that it is likely to achieve a good result.

14. Summary

Four hundred and fifty-seven patients who had unilateral AP treatment for cavitated disease were followed up for a minimum period of eight years; only 1.13% were lost from observation. Statistical analysis of this group leads to the following conclusions :

i. In selected cases, unilateral AP can achieve excellent results that have not yet been superseded.
ii. Cavity closure, not freedom from adhesions, is the key to successful pneumothorax treatment. Adhesions that do not prevent cavity closure have no effect on the prognosis.
iii. It is reasonable to supplement AP treatment with the use of antibacterial drugs in the hope of obtaining even better results in the future.

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Book Reviews

Tuberculosis in Childhood and Adolescence, with Special Reference to the Pulmonary Forms of the Disease

F. J. Bentley, S. Grzybowski & B. Benjamin. London: National Association for the Prevention of Tuberculosis, 1954. xii + 259 pages; 36 illustrations. 25 × 17 cm. £1 10s.

This admirable book is based on a follow-up for an average period of six years of over a thousand children either with primary tuberculosis and chest *x*-ray abnormalities, or with the adult type of pulmonary lesions. All were treated in High Wood Hospital, Brentwood, Essex, and came from the area administered by the London County Council.

Hospital patients suffering from primary tuberculosis are a highly selected group. Although they do not provide a fully representative picture of the disease, these patients are a most valuable source of information on the more severe forms. The authors fully appreciate both the advantages and the limitations of their material, and their analysis is direct and lucid.

Because it was certain that many children died without having been admitted to High Wood Hospital a special study of 100 consecutive deaths from tuberculosis in children in the London area was made. This study includes an assessment of the proportion of the deaths that might have been avoided by preventing the primary infection, by earlier diagnosis or by more efficient treatment. The gloomy conclusions of this part of the book give much food for thought.

The cases of primary disease have been classified as simple primary tuberculosis, segmental lesions, pleural effusions, miliary tuberculosis, and quiescent primary lesions. Under each of these headings the incidence, clinical features, diagnosis, course, prognosis and treatment of the disease are presented, and the important findings are summarized at the end of each chapter. The result is more than an analysis, it is a textbook.

Many additional points of interest are discussed and illuminated, such as the prognostic significance of erythema nodosum, the importance of enlargement of paratracheal glands, and the influence of measles and whooping cough. The section on primary disease concludes with a chapter on management which offers balanced guidance on the practical application of the information obtained from the survey.

The section on chronic pulmonary tuberculosis deals with over a hundred patients, representing nearly every case diagnosed in London in children under the age of 15 during the period of the survey. The findings are in vivid contrast to those for primary disease. The book concludes with a discussion of the relationship of the two types of disease and the most valuable criteria for differentiating between them.

The book is well produced, the many tables are clearly set out, and the standard of *x*-ray illustration is good, although it would be much more convenient if the illustrations were nearer to their text references instead of being in a separate section. The appendices include one on epidemiology, and there is an adequate bibliography.

This is a most valuable addition to the literature on tuberculosis and should be carefully studied by every paediatrician and chest physician. It is a book which will be referred to again and again.

Wallace Fox

A Practice of Thoracic Surgery

A. L. d'Abreu. London: Edward Arnold & Co., 1953. viii + 591 pages; figures. 26 × 19 cm. £4

In this book Mr d'Abreu describes all the various conditions that are met in the practice of thoracic surgery, and while, as he points out in the preface, he describes his own practice at the present time, this does not differ materially from that of most thoracic surgical units in Great Britain, or, for that matter, in the United States of America.

The book is excellently set out, and it is very easy to find one's way about it. The subject lends itself well to a broad basic division. Each chapter, dealing with a single condition, or group of allied disorders, is split up into clearly marked sections on aetiology, pathology, diagnosis, treatment, etc., and each chapter has a broad general introductory paragraph. The illustrations are of a very high order; in particular the reproductions of radiographs deserve special mention. The sub-titles to the illustrations are clear and concise. The list of references at the end of each chapter, while not exhaustive, gives the details of the acknowledged authoritative relevant publications.

The book will be of value to general physicians and surgeons, paediatricians, pathologists and radiologists, and others whose work is interwoven with that of the thoracic surgeon. They need not fear to look in this book for the information they require, for they will find it without difficulty, unencumbered by surgical technical detail, which is always relegated to its own section. Practising thoracic surgeons will not find it of so much value, for, as Mr d'Abreu says, they should know it all already. But even so, they will find much of interest. The book will be invaluable to those undergoing training in thoracic surgery, to those who have recently completed their training, and to postgraduate students for higher surgical degrees.

There is little to criticize; there are a few errors of description of illustrations, but these are of little importance. Everything that Mr d'Abreu has written is sound, and eminently readable. His style is a welcome change from the technical jargon in which so many medical publications are presented.

The section dealing with the diagnosis of carcinoma of bronchus is not up to the high standard of the rest of the book, and could have been more clearly set out. I would also have liked Mr d'Abreu, with his great experience, to have given more space to the introductory paragraphs of the chapters, and dealt at greater length with the broad aspects and "policy" of treatment of the different conditions; he could have done so at the expense of descriptions in detail of technical surgical procedures, for these latter cannot be learnt from a book, but only by seeing, assisting, and doing them. But these are minor and personal criticisms. The book is a valuable one; Mr d'Abreu has made many important contributions to thoracic surgery, and this book is by no means the least of them.

Kenneth S. Mullard

The Principles of Thoracic Anaesthesia Past and Present

William W. Mushin & L. Rendell-Baker. Oxford: Blackwell Scientific Publications, 1953. xviii + 172 pages; 217 figures. 25 × 19 cm. £2 2s.

There can be little gainsaying that the title of this book is misleading. In fact, "the principles of thoracic anaesthesia" which, after all, differ little from the principles of any other forms of anaesthesia, are hardly discussed at all. These pages contain little reference to the pharmacological advances that have made such a difference to all forms of anaesthesia, and what there is will be found in the last chapter of some seven pages, which includes a superficial discussion of the anaesthetic agents and techniques which have been used in the past and are employed at present. Furthermore, one would look in vain for any description of local anaesthetic techniques for thoracoplasty, or any attempt to assess their value as compared with that of general anaesthesia, and an even more notable omission is in reference to the revolution in the technique of general anaesthesia for endoscopies which has occurred since the introduction of relaxant agents. All these features, and others, which might be expected in a book on thoracic anaesthesia, the authors have deliberately eschewed. They state at the outset in their preface that "This is not a 'how-to-do-it' book", and, in assessing the result of their labour, one must accept the limited field they have chosen. A reviewer must, however, question the

misleading title—it would have been more descriptive and accurate to call this volume *The mechanical principles of thoracic anaesthesia.*

On the ground they have chosen to cover, the authors have produced an intriguing and valuable book. The first section of some 25 pages is a simple and almost naïve review of the problems posed by the open chest, and their solution—controlled respiration. Chapter IV, which is included in this section and is of two-and-a-half pages, will serve as a valuable instruction to those concerned with care of the " water seal " type of drainage. The second part of the book, which includes the next 16 pages, covers the historical background of the subject, but not completely, because in the final part, " Methods in use today ", which is the bulk of the volume, history still forms a great part of the text and of the illustrations. This latter section is concerned with the evolution of automatic devices for rhythmic inflation of the lung and methods of tracheal and bronchial intubation, and of the control of secretions. It is a feature throughout that the old and the new are brought into challenging juxtaposition, and the lesson, surely, that the book will teach is that of humility, for a perusal of these pages will impress on one that there is little new, even in the most advanced ideas.

In the final appendix there are 33 short but interesting biographies and miniature photographs of some of the outstanding pioneers in the development of modern thoracic surgery and anaesthesia.

This volume will fill gaps in the background of many anaesthetists and, indeed, physicians and surgeons interested in thoracic work. Practitioners engaged in the young specialty of anaesthesia have, in their days of training, little leisure to delve into the past of their fascinating subject. After qualification and achievement of consultant status their life becomes caught up in the maelstrom of increasingly longer hours in the operating-theatre, and their leisure is too rare and precious to encourage them, or even permit them, to explore the ever-intriguing by-roads of history. Clearly, they could not do better than purchase this book, which certainly on the historical side will remain a reference work for many years to come.

The text is lucidly and clearly illustrated and excellently printed, which accounts for the rather high price : but it is a sound purchase for thoracic anaesthetists, surgeons, and, indeed, physicians.

T. C. Gray

Pneumoconiosis Abstracts. Volume I. Reprinted from the *Bulletin of Hygiene* for the Years 1926 to 1938 Inclusive, by Permission of the Honorary Managing Committee of the Bureau of Hygiene and Tropical Diseases

Bureau of Hygiene and Tropical Diseases. London: Sir Isaac Pitman & Sons Ltd., 1953. xi + 347 pages; figures. 25 × 19 cm. £3 3s.

These abstracts were collected and published at the suggestion of Professor E. J. King of the Postgraduate Medical School of London, well known for his investigations on pneumoconiosis. The Medical Research Council supported Professor King's proposal and contributed to the cost of the publication. Research workers and others interested in pneumoconiosis have cause to be grateful for this valuable volume which covers the years 1926–38 inclusive. A second volume will cover 1939–50.

For many years the *Bulletin of Hygiene* has provided abstracts on pneumoconiosis by experts in this field. Dr E. L. Middleton undertook the task of selecting the relevant abstracts and also of compiling the indexes. As a basis for his selection Dr Middleton used the broad definition of pneumoconiosis suggested by L. U. Gardner: "All forms of pulmonary reaction to inhaled dust, with no implication as to character, severity or effect on function". In this definition the word " dust " is used to include fume in the solid state. Pulmonary reaction is taken to include pneumonitis but not allergic reaction unless where some important structural pulmonary change follows directly from the inhaled dust. Systemic effects of chemical poisons or of living organisms are excluded. Cancer is included where a connexion is claimed between the inhaled dust or diseases caused by it and the formation of the new growth.

The subjects dealt with are arranged in 12 sections and include silicosis, asbestosis, pneumoconiosis of coal-workers, pneumoconiosis caused by other inorganic dusts, that caused by dusts of vegetable origin, and that caused by fumes. There is a section on sampling and measurement of atmospheric dusts, and studies of their physical, mineralogical and chemical properties, and one on methods of suppression and removal of dust, and on personal respiratory protection. Other sections cover legislation on pneumoconiosis and give summaries of periodical reports, including those of the Chief Inspector of Factories and Workshops, the Safety in Mines Research Board, the Mines Department, Department of Scientific and Industrial Research, Medical Research Council, International Labour Office, the Miners' Phthisis Medical Bureau of South Africa, the South African Institute for Medical Research and the Commonwealth of Australia Division of Industrial Hygiene. These abstracts of reports are particularly valuable, as the original publications are in some cases difficult to purchase or even to borrow.

The names of the original abstracters are given with each abstract. This will give the reader increased confidence in their accuracy, as the names are of experts in the field of industrial pulmonary diseases, and particularly prominent are those of E. L. Collis and the late S. Roodhouse Gloyne and S. Lyle Cummins. There are a number of book reviews and accurate separate indexes of authors and subjects.

The material in this volume is not only of historical interest but is also of great value in relation to contemporary problems, as in some instances investigators today are no nearer a solution than were the workers of a quarter of a century ago, whose views and discussions will repay careful study.

J. Gough

Milk Pasteurization: Planning, Plant, Operation, and Control

H. D. Kay, J. R. Cuttell, H. S. Hall, A. T. R. Mattick & A. Rowlands. Geneva: World Health Organization, 1953. (World Health Organization Monograph Series No. 14.) 204 pages; 93 figures. 24 × 16 cm. 12s. 6d.

The publication of this important monograph, dealing as it does with all aspects of milk production, is timely. Sales of pasteurized milk are continually increasing. It is essential that milk processed in this manner should be handled efficiently if success is to be achieved and public health suitably safeguarded.

While not purporting to be exhaustive, the volume contains up-to-date information on premises and plant, together with the methods required for milk pasteurization, surveying the entire field of present knowledge of the process. Indeed, it goes further, in that the importance of the methods employed are stressed, while the dairy buildings and the various types of plant are suitably described. Plant operation is given detailed consideration and, what is probably most important of all, a description of the various tests for raw and pasteurized milk and of the control of processing is included. Control methods are given due prominence. An admirable bibliography completes the volume, providing information for further detailed study.

This monograph is recommended to all interested persons, not only as a guide for public bodies and controlling officials, but also to assist those responsible for the day-to-day pasteurization of milk.

W. C. Harvey

Advances in the Control of Zoonoses: Bovine Tuberculosis — Brucellosis — Leptospirosis — Q Fever — Rabies. WHO/FAO Seminar on Zoonoses, Vienna, November 1952

World Health Organization and Food and Agriculture Organization. Geneva: World Health Organization, 1953. (World Health Organization Monograph Series No. 19.) 275 pages; figures. 24 × 16 cm. 15s.

" Zoonoses " is a relatively new term designating diseases that are transmitted naturally between vertebrate animals and man. It will thus be seen that the control of zoonoses presents a major problem to veterinarians and to public health. The above monograph represents the collected results of a seminar held in November 1952, in Vienna. This seminar was convened by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations and was attended by a representative selection of medical and veterinary specialists from many countries. The publication of this monograph will be

welcomed as representing a composite expression of current opinion relating to this important subject.

The first section, devoted to bovine tuberculosis, is particularly interesting and should be of the greatest value. The remaining sections, which deal with brucellosis, leptospirosis, Q fever and rabies should be found of equal benefit.

The monograph is well produced and easily readable. Each of the sections contains a useful list of references. Altogether, those responsible for the publication of *Advances in the control of zoonoses* are to be congratulated.

W. C. Harvey

A Synopsis of Children's Diseases

John Rendle-Short. Bristol: John Wright & Sons Ltd., 1954. xii + 608 pages; 7 figures. 19 × 13 cm. £1 12s. 6d.

A Synopsis of Anaesthesia

J. Alfred Lee. 3rd ed. Bristol: John Wright & Sons Ltd., 1953. vi + 483 pages; 72 illustrations. 19 × 13 cm. £1 1s.

The Synopsis Series of publications has enjoyed a well-earned popularity for many years, especially among those preparing for examinations. They are designed for quick reference and revision and are not intended to replace standard textbooks; they suffer from the deficiencies of a synopsis but include a remarkable amount of useful information in a small compass. The usual high standard is maintained in the present volumes.

In the volume on children's diseases, two chapters are devoted to tuberculosis in childhood and cover adequately the clinical field, but the natural history of the disease, its prevention and sociological aspects receive scant attention. In connexion with chemotherapy, isoniazid (isonicotinic acid hydrazide) receives no mention and calciferol, which is still used with advantage at many centres, is not included under the treatment for cervical adenitis. One of the disadvantages of abstracting from textbooks is the perpetuation of existing fallacies, and once again pulmonary tuberculosis is stated to be rare among persons suffering from mitral stenosis, whereas it has, in fact, been demonstrated that the incidence is no less than in the general population. In the section dealing with erythema nodosum (part of a systemic infection), coccidioidomycosis, a rare disease in Great Britain, is listed in addition to tuberculosis and rheumatism as a possible cause, while more common conditions are omitted. Apart from these minor deficiencies, the material is well and accurately presented and fulfils the purpose for which it was written. Drug dosage and normal biochemical values have been included conveniently as appendices.

The volume on anaesthesia has been completely revised since the last edition was published in 1950; two new chapters have been added and many new figures included. The book is up to date and detailed and ranges over the whole field of anaesthetics. The chapter dealing with anaesthesia in thoracic surgery outlines the special problems involved and there are separate sections devoted to thoracoplasty and lung resection. The hazards of open pneumothorax are adequately discussed. Anaesthetics for intrathoracic non-pulmonary operations, including all forms of cardiac surgery, are outlined satisfactorily. Topical anaesthesia for bronchography, bronchoscopy and oesophagoscopy are described in their appropriate sections and the use of oxygen in anaesthesia and treatment is described in the early part of the book. The hazards of high oxygen atmospheres are rightly emphasized and the rationale is briefly explained. Although written mainly for those with a special interest in anaesthetics there is much in this book of general interest and practical value.

Philip Ellman

French's Index of Differential Diagnosis

Edited by *Arthur H. Douthwaite.* 7th ed. Bristol: John Wright & Sons, Ltd., 1954. xii + 1046 pages; 731 illustrations. 26 × 17 cm. £5 5s.

Once again we have a new edition of that tried, trusted and almost traditional volume that was first published by Dr Herbert French in 1912, under the title of *An index of differential diagnosis of main symptoms.* Since the publication of the 6th edition Dr French himself has died and the sole responsibility of editorship has now devolved on Dr A. H. Douthwaite, Senior Physician at Guy's Hospital.

Dr Douthwaite, himself a true follower and teacher of the clinical approach to disease, has considerably altered the lay-out of this 7th edition, thus avoiding much of the overlapping and over-elaboration that was apparent in the previous editions. A number of new contributors also make their appearance, as some of the earlier ones have died. One notices with interest that several of the sections have been rewritten rather than revised, in order to incorporate new and up-to-date material. This revision is all the more welcome because recent developments in methods of investigation and accessory aids to diagnosis—such as gastroscopy, biochemical tests and spectrum analysis—are now available.

Although some of the plates and pictures are old, their improved reproduction in this new edition seems to enhance their value. Particularly commendable is the section on the anaemias by Dr Waterfield, in which the coloured plates are most effective and the letter-press fully comprehensive. The illustrations in the sections on the eye, supervised by Mr Frank Law, are also cleverly and artistically tinted, giving a realistic impression of the conditions represented.

Dr Douthwaite has certainly chosen his team of collaborators well. The practised hand of Sir Adolphe Abrahams deals with many items included under the headings of ascites, alimentary disorders, abdominal pain, fevers and pyrexia; while the orthopaedic aspects are effectively handled by Sir Heneage Ogilvie with the co-operation of Mr Hedley Atkins. Dr Scadding handles the section on chest deformities and effusions with considerable skill. His new series of *x*-ray pictures in positive—as opposed to negative—relief, though small, are very clear. To some of us, however, the negative definition still seems more acceptable, though this of course is an individual view.

When we come to the question of pulmonary tuberculosis, we find it necessary to wade through numerous references in order to sort out the various manifestations of this disease. It appears under such headings as causes of anaemia, fatigue, loss of weight, pyrexia, cough, haemoptosis, and anorexia, while surgical tuberculosis of glands, bone and various organs occurs under the separate headings of those particular organs. This symptomatic treatment of such an important disease is, of course, extremely effective from the point of view of "differential diagnosis", but hardly perhaps adequately stresses the importance of the disease as an entity, if indeed we are to regard it as such. If any further criticism seems justified, perhaps it is that the heart conditions so well dealt with by Dr Gavey seem to overshadow the other chest diseases.

The neurological diseases are certainly very extensively dealt with, and it is interesting to see, under the causes of polyneuritis—poisoning from the wood-tick, potassium intoxication and Pink disease, the latter attributed to mercury poisoning, but without reference to the use of teething powders and grey powders. [As the editor says, "The truth is not yet known".]

The present volume, although still bulky, is by no means as weighty as its two predecessors. The editor and his publishers are to be commended for the condensation they have achieved, while still maintaining this edition as one of the standard reference textbooks for medical students and practitioners that can be strongly recommended. The index is clear and comprehensive, while the methods of tabulation employed in the text afford an easy form of effective comparison of the main symptoms and signs of the common diseases.

R. Cove-Smith

Antibiotics

F. A. Robinson. London: Sir Isaac Pitman & Sons Ltd., 1953. viii + 132 pages. 22 × 14 cm. 15s.

The author who tries to cover the whole subject of antibiotics in a short book sets himself an impossible task: in confining himself to the scientific aspects of his subject and omitting the clinical or veterinary applications, the author of this book has produced a clear and well-balanced account.

This book is devoted mainly to the clinically important antibiotics—penicillin, streptomycin, chloramphenicol, aureomycin and terramycin—but chapters are also included dealing with other antibiotics, whether or not they are important in medicine. The chemistry and commercial production of these substances are fully discussed, and an adequate account is given of their pharmacology and bacteriology, although the medical bacteriologist, perhaps, might wish for a fuller consideration of bacterial resistance.

The bibliography lists chiefly textbooks and review articles, and a few of the most important early papers: detailed references to the literature are not given.

In a rapidly advancing subject such as this, a concise survey is needed from time to time by an author who has read widely: this book fulfils well that need. To the scientific worker who wishes to keep abreast of recent advances and to the doctor who wishes to know something of the scientific background of an important group of therapeutic substances, this short work is thoroughly to be recommended.

G. W. S. Andrews

World Directory of Medical Schools

World Health Organization. Geneva: World Health Organization, 1953. 220 pages. 24 × 16 cm. £1 5s.

A book consisting of a list of the medical schools thoughout the world sounds a dull affair, but it is full of interest for any that seek it out. The World Health Organization has not only listed over 500 schools but has presented in tabular form brief information about each—how administered, whether by a government department, a university or a private corporation, the length of the academic year, the conditions of admission, the number of the teaching staff, the number of students, the number of annual admissions, the language of instruction, the duration of the curriculum, the degrees or diplomas obtainable and the annual number of graduates. Not all these details have been obtained for every medical school, and for those in the Union of Soviet Socialist Republics only the names of the schools are given, but it is remarkable how few gaps there are, considering the ambitious nature of the project. The schools are given under the names of the countries and these are arranged alphabetically. The number of schools in the different countries varies from one to seventy-nine. In several small countries such as Haiti and Peru, there is, as might be expected, only one; in the United States of America there are seventy-nine. There are three schools that admit men only, one each in Mexico and India and the sole school in Afghanistan, but there are considerably more that take women only, though these are in no instance the only school in the country.

Perhaps the most interesting impression obtained from this book is the uniformity of requirements before a medical practitioner is licensed to practise. These are roughly six years of pre-clinical and clinical study following the attainment of a satisfactory standard of knowledge of physics, chemistry and biology, or four years following three years of "college" with perhaps a B.A. or a B.Sc. as a result of these three years. The medical school curriculum results in the degree of M.D. in most American schools and in that of M.B. in those of the United Kingdom and the schools with a British foundation, but in most schools in the continent of Europe or following the European tradition the normal curriculum gives only a licence to practise and the doctorate of the university requires a thesis in addition.

This compilation is a milestone in the literature of the history of medical education in spite of its resemblance to a catalogue, for it records the advent of something approaching a common course of study throughout the world before a licence to practise medicine can be granted. For any person who deals with graduates from many countries it should prove a valuable work of reference and as the obvious gaps are filled in subsequent editions it will be emblematic of a happier world and of the universal fraternity of medicine that knows no boundaries.

Francis R. Fraser

Stedman's Medical Dictionary

of Words used in Medicine with their Derivations and Pronunciation including Dental, Veterinary, Chemical, Botanical, Electrical, Life Insurance and other Special Terms; Anatomical Tables of Titles in General Use, the Terms Sanctioned by the Basle Anatomical Convention; the New British Anatomical Nomenclature; Pharmaceutical Preparations Official in the US and British Pharmacopoeias or contained in the National Formulary; Biographical Sketches of the Principal Figures in the History of Medicine. Edited by *Norman Burke Taylor* in collaboration with *Allen Ellsworth Taylor.* 18th revised ed. London: Baillière, Tindall & Cox Ltd., 1954. xliv + 1561 pages; illustrations. 25 × 17 cm. £3 3s.

When we were very young, our professor of anatomy used to begin his course by saying, "Some of you may not have had the advantage of a classical education. I would advise these persons to procure second-hand Greek and Latin grammars and study the elements of the languages, so that they may avoid making ludicrous mistakes in medical terminology". That was over 25 years ago, and in the meanwhile the incidence of classical scholars in medicine has gone steadily down, and the incidence of ludicrous mistakes has gone up. It is good to see an effort being made to reverse this trend in the latest edition of "Stedman".

The present editors, who, as Canadians, enjoy the happy privilege of standing midway between United States iconoclasm and United Kingdom traditionalism, attempt in a preface to impart the rudiments of medical Latin and Greek to the coiners of medical terms. It was a good idea to divide the editorial work between a physician and a classical scholar, and our sympathy goes out to them when they plead for a mixed committee of medical men and authorities on the classics to adjudicate on new terms. On one point, however, they have had to surrender. They complain that Greek loses its personality when transliterated. This is true of all transliterations, as witness the unpleasing appearance of Polish words in comparison with Russian. Nevertheless, they have felt obliged to transliterate in this dictionary.

This edition is said to contain several thousand new words, and should prove entirely satisfactory to its users. If a criticism is to be made, it should be of some of the illustrations, whose value is open to question. It is doubtful, for example, whether the sketches of "chemosis" and "ectropion" would really help the novice much. The sketch of "myositis ossificans" has little to recommend it, and the patient with "diffuse lipoma" might well be wearing a beard rather than a collar of fat. These strictures apply, of course, to other dictionaries as well as "Stedman". Perhaps the wisest plan is to omit all pictures not essential to the text.

S. S. B. Gilder

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TUBERCULOSIS CONGRESSES 1954

British Tuberculosis Association

ANNUAL CONFERENCE. 7–10 July 1954, Oxford. *The Secretary:* British Tuberculosis Association, 16 Grosvenor Place, London, S.W.1

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International Union Against Tuberculosis

THIRTEENTH CONFERENCE. 26 September–2 October 1954, Madrid. *Secretariat:* Escuela de Tisiologia, Ciudad Universitaria, Madrid

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International Congress on Diseases of the Chest

III CONGRESO INTERNACIONAL DE ENFERMEDADES DEL TÓRAX del "American College of Chest Physicians". 4–8 October 1954, Barcelona. *Secretario General:* Dr A. Caralps, Córcega, 393, 4º, 1ª, Barcelona

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ADDENDUM: "Gas gangrene", *Brit. med. Bull.* 1954, **10**, 52–58

Professor C. L. Oakley points out that in this article he misinterpreted Dr M. G. Macfarlane's paper (1945) quoted there, and also omitted to mention her much more thorough paper (1943) on the value of antitoxins in treatment. He asks, accordingly, that readers should delete from " It is exceedingly difficult " (p. 56, col. 2, line 3) to " of no value " (line 26) and substitute the following:

" It is exceedingly difficult to disentangle the effect of either form of treatment from the effect of surgery in human cases. Animal experiments (Gordon & McLeod, 1941) suggest strongly that antitoxin in relatively small amounts has a marked prophylactic effect, and it is the general view that antitoxin is a useful adjunct to surgery and chemotherapy (MacLennan, 1943c). MacLennan himself was convinced that antitoxin was of value in treatment, though he admitted that the number of cases he then had did not justify more than an opinion. The only thorough investigation is that of Macfarlane (1943) who showed that administration of large amounts of polyvalent antitoxin from 0 to 6 hours after diagnosis greatly reduced the mortality of unselected toxaemic cases that had received adequate surgical treatment; if antitoxin was given more than 6 hours after diagnosis, it had no effect.

The results obtained were much the same whether gas gangrene was established when patients were admitted to hospital, or the disease developed in hospital; one must assume that established cases were brought in very soon after development of the disease. Surgery alone had little effect in reducing the mortality, and antitoxin alone probably none at all. Though these conclusions were supported by MacLennan & Macfarlane (1944) and Macfarlane (1945), the views of other workers have been less favourable. Jeffrey & Thomson (1944) were doubtful of the value of antitoxin, and state that its use does not affect the death-rate; Langley & Winkelstein (1945) thought that it had some postoperative, but no pre-operative value. North (1947) considers that it is of no value ".

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